Bio-Cardiozyme Forte® & Bio-Cardio Packs®

The cardiovascular system, consisting of the heart, network of blood vessels, capillaries, arteries, and arterioles, cumulatively represents a network many miles long. The cardiovascular system distributes nutrients, including oxygen, to all cells of the body, and it also functions to remove metabolic wastes. It serves as a cooling system, as a defense system via humoral and cell mediated immunity, and as a communication system (endocrine system) to maintain homeostasis. Its electrolytes maintain fluid and pH balance in all compartments of the body. Consequently, normal function of the cardiovascular system requires the integration of many bodily organs.

Cardiovascular disease (CVD) is responsible for the majority of deaths in the US, and coronary heart disease (CHD) accounts for almost 50% of the cardiovascular mortality. Thus a malfunction of the cardiovascular system forms a basis for degenerative type diseases. CHD is the major cause of premature death among men and women, thus CHD represents a modern epidemic.[1] Cardiovascular disease is a multifactorial condition. Well-established risk factors include both genetic and lifestyle aspects. Non-modifiable factors, otherwise noted as inheritance factors, are male gender, family history of CHD and menopause. Risk factors associated with medical history include cigarette smoking, uncontrolled diabetes mellitus, uncontrolled hypertension, obesity, high serum cholesterol (dyslipdemia) and elevated serum homocysteine.[2]

Lifestyle Functions

A wide variety of lifestyle factors influence the risk of CHD. Cigarette smoking, physical inactivity and a diet high in saturated fats, all play a role in the prevalence of cardiovascular disease in the U.S. A high intake of linoleic acid (N-6 polyunsaturated fatty acids) and certain saturated fatty acids adds to the risk.[3] Thus, lifestyle modifications offer the likelihood of decreased risk and improved health. Interventions include diet modification, regular exercise and pharmacologic approaches when needed.[2] Recommended dietary modification for the prevention of cardiovascular disease include a diet that provides less than 30% of daily calories from fat (some experts recommend 20%), with saturated fats consisting of 8–10% of the daily caloric value; less than 300 mg cholesterol daily; and moderate amounts of sodium — equivalent to a maximum of 2.4 g daily. Excessive trans fatty acid consumption may also be correlated with cardiovascular dysfunction.[4] In addition, excessive alcohol consumption has shown to contribute to an increased risk, thus limiting alcohol consumption is typically included as a recommended guideline. Other evidence indicates that foods rich in N-3 polyunsaturated fatty acids from fish, along with vegetables lower the risk of cardiovascular disease. Trace minerals and fiber also have documented benefits for maintaining cardiovascular health.[5]

Nutritional Support for Cardiovascular Health

Nutritional support of the circulatory system is multifaceted. Optimal functioning of the cellular machinery requires a balance of key nutrients, including building blocks, enzyme cofactors, antioxidants and essential fatty acids, for maintenance of the cellular mechanisms. It has been suggested that the failure of the heart, along with subsequent myocardial infarction, "may be associated with an antioxidant deficit as well as increased myocardial oxidative stress."[6]

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Antioxidants

The oxidation hypothesis of atherosclerosis postulates that the oxidative modification of lipoprotein, in particular low-density lipoprotein (LDL), increases the risk of atherosclerosis via alteration of receptor-mediated uptake by cells, particularly of those located in the intima of blood vessels. As a result, an uncontrolled process ensues, whereby oxidized LDL is taken up by scavenger receptors on monocytes, macrophages, and smooth muscle cells, leading to lipid accumulation and the formation of foam cell, an early attribute of atherosclerotic plaque.[7]

Vitamin E - Vitamin E is the major lipid-soluble antioxidant in cell membranes and serum lipoproteins. The primary role of vitamin E appears to prevent lipid peroxidation, particularly polyunsaturated fatty acids. Low vitamin E status is linked to an increased risk of cardiovascular disease and other degenerative diseases related to oxidative stress.[8] Vitamin E has been shown to protect LDL peroxidation *in vitro*. Furthermore, a prospective study demonstrated that supplementation with vitamin E reduced the risk of nonfatal myocardial infarction in patients with established cardiovascular disease.[9] As an added benefit the natural vitamin E is emulsified for enhanced absorption.

N-Acetylcysteine - N-Acetylcysteine (NAC) is a cysteine derivative. It is readily absorbed and hydrolyzed to release cysteine, which in turn serves as a precursor of glutathione synthesis. Reduced glutathione functions as a major cytoplasmic antioxidant, and may be conjugated with a variety of toxic materials as part of the body's detoxification mechanisms. Orally administered NAC can increase plasma levels of cysteine, as well as tissue levels of glutathione.[10] Interaction of thiols, including glutathione, can increase antioxidant defenses.[11]

Vitamin C (Ascorbic Acid) - Vitamin C represents a major water-soluble antioxidant of plasma. It serves as a scavenger of a wide range of reactive oxygen species, including lipid peroxyl radicals and the superoxide radical. Vitamin C is an effective antioxidant in plasma.[12] In studies subjecting human plasma to free radicals, vitamin C was demonstrated to be the first antioxidant diminished, indicating its free-radical quenching ability.[13] Vitamin C was also shown to favorably alter the lipoprotein pattern in young women,[14] and to limit LDL oxidation *in vitro*.[15] It was also shown to aide in the non-enzymatic regeneration of alpha tocopherol.[16] Reduced glutathione seems to be a key in regenerating ascorbate.[17] Vitamin C is used to convert cholesterol to bile salts, thereby assisting in the long-term removal of cholesterol. Furthermore, vitamin C acts as a co-substrate for catecholamine synthesis,[18] carnitine synthesis and for collagen synthesis. Subsequently, Vitamin C deficiency decreases vascular integrity, due to its requirement in collagen synthesis and proteoglycan synthesis. Studies have indicated a dietary range of 100 to 400 mg per day for young, healthy males.[19]

Selenium - As a cofactor for glutathione peroxidases, selenium is considered an antioxidant nutrient. The predominant chemical form of selenium in grains, such as wheat, is selenomethionine. Selenomethionine is converted to selenocysteine, which is incorporated into enzymes. A vegetarian diet does not generally provide adequate levels of antioxidant minerals, especially selenium.[20] Glutathione peroxidases remove cytoplasmic hydrogen peroxide, and inactivate lipid peroxides. Additionally, selenium and vitamin E have been shown to have synergistic effects.[20,21] In **Bio-Cardiozyme Forte®** selenium is provided as a food source rather than as an inorganic form.

Natural mixed carotenoids - The consumption of foods rich in carotenoids is linked to the reduced risk of many chronic health conditions. Beta-carotene has been shown to inhibit lipid peroxidation of cell membranes.[22] In addition to beta-carotene and other carotenes, **Bio-Cardiozyme Forte®** and **Bio-Cardio Packs®** also contain natural mixed carotenoids along with oxidized carotenoids such as cryptoxanthin and lutein. Functionally, carotenoids act as antioxidants by their ability to quench free radicals and reactive oxygen species, especially singlet oxygen.[23] In this sense, they complement vitamin E. Studies have indicated that natural, mixed carotenoids are better absorbed and are more effective antioxidants *in vivo* than the usual synthetic beta-carotene.

B Complex Vitamins

Thiamine pyrophosphate, riboflavin 5-phosphate and vitamin B6-phosphate - These B-vitamins are the "activated" forms of thiamine, riboflavin and vitamin B6, respectively. Combined with phosphate, they serve coenzyme functions. Thiamine, riboflavin, niacin and niacinamide work together in enzyme systems that convert fuels to energy, the Krebs's or citric acid cycle. As a result of highly commercialized and processed food, insufficient dietary intakes of B vitamins, folic acid and pyridoxine has been noted, corresponding to elevated levels of blood homocysteine and vascular disease, as postulated by the homocysteine theory of arteriosclerosis.[24]

Vitamin B6 - Vitamin B6 is found naturally as three distinct, interconvertible forms, pyridoxal, pyridoxine or pyridoxamine, which are the aldehyde, alcohol and amine forms, respectively. Greater than one hundred reactions are dependent upon pyridoxal as a coenzyme, including the synthesis of the neurotransmitters GABA, serotonin, dopamine, norepinephrine and epinephrine. Significant amounts of vitamin B6 are contained within various tissues, including the heart, liver, brain, spleen and kidney, however since there is no storage mechanism, the vitamin must be presented daily in the diet.[25] The intake of vitamin B6 has been correlated with the inhibition of platelet aggregation, devoid of effecting platelet count, and also with prolonged clotting time. In reference to both total plasma lipid and cholesterol levels, pyridoxine was shown to significantly reduce these levels, and to enhance HDL-cholesterol levels in normal subjects. Additionally, this same study concluded that pyridoxine supplementation significantly increased ($p < 0.001$) serum zinc levels.[26]

Vitamin B6 also plays a role in the conversion of homocysteine. As an intermediate in the biosynthesis of cysteine from methionine, homocysteine is considered a vasculotoxic and a thrombogenic amino acid. This conversion relies on the enzyme cystathionine beta synthase, which requires pyridoxal phosphate as a cofactor. Elevated plasma homocysteine is a confirmed risk factor for vascular disease.[27,28]

Regardless of age and sex it has been established that the risk of coronary disease rises proportionately with increasing concentrations of plasma homocysteine.[27] Furthermore, low pyridoxal phosphate is deemed as an independent risk factor for coronary artery disease. Along with red blood cell folate and cobalamin, low pyridoxal phosphate has been correlated with the occurrence of early onset coronary artery disease,[29] while an increase in vitamin B6 and folate were shown to lower plasma homocysteine.[30] Correspondingly, it has been estimated that a high plasma homocysteine concentration is associated with an inadequate plasma concentration of one or more B vitamins approximately 67% of the time, and along with folate, plasma concentration of pyridoxal-5-phosphate is inversely associated with carotid stenosis.[31]

Thiamine - Thiamine is part of the coenzyme cocarboxylase, otherwise know as thiamin pyrophosphate (TPP), which is a required enzyme in the metabolism of carbohydrates. Carbohydrate metabolism is a three-stage process, which in the absence of thiamin as part of the coenzyme TPP results in a slowing or complete blocking of the reactions.[25]Thiamine also plays an active part in citric acid cycle in the decarboxylation of a-ketoglutaric acid to succinayl CoA, as well as in gluconeogenesis as part of the thiamine dependent enzyme transketolase. A disturbance in glucose metabolism has been associated with thiamin deficiency, which was reversed once the deficiency was corrected.[32] Additionally, a significantly linked correlation has been documented between thiamin deficiency and heart disease.[33]

Niacinamide - Niacinamide is an integral part of the coenzymes NAD and NADP, which transfer electrons in key oxidation-reduction reactions, thus function in the redox state of the cell.

Niacin - Niacin possesses physiologic properties in addition to serving as a redox agent. Studies have indicated that niacin plays a role in the support of serum cholesterol levels in certain people,[34,35] and has also been correlated with a significant increase in HDL cholesterol.[36] Its vasodilation properties are the basis for a warm, tingling sensation that sometimes accompanies skin flushing.

Biotin - Biotin plays an integral part in metabolic pathways, including gluconeogenesis, fatty acid synthesis and amino acid catabolism. As part of its function Biotin acts as a cofactor to aid in the transfer of CO2 groups to target molecules. In humans biotin is associated with four enzymes, pyruvate carboxylase, b-Methylcrotonyl-CoA carboxylase, Propionyl-CoA carboxylase and Acetyl-CoA carboxylase.[37] As part of its function with these enzymes, it assists the liver in maintaining adequate blood sugar levels, and in the formation of fatty acids from carbohydrates. Biotin also serves as a cofactor for phosphylase, the enzyme that degrades glycogen, and it is a required component for carboxylation enzymes, which serve to convert carbon dioxide to glucose via oxaloacetate by the action of the enzyme pyruvate carboxylase.

Vitamin B12 - Vitamin B12 supports nucleic acid synthesis and helps to maintain peripheral nerves. Together vitamin B12 and folic acid support the use of methionine as a methylating agent, and the conversion of homocysteine to methionine. Hyperhomocysteinemia is recognized as a putative independent risk factor for cardiovascular disease[38,39,40] and elevated homocysteine concentrations have been correlated with increased odds ratio of coronary heart disease.[40] Elevated homocysteine has also been associated with damage induction to the vascular walls, either directly or via the generation of reactive oxygen species.[41] Even moderate hyperhomocysteinemia has been associated with cardiovascular risk factors including atherosclerosis, thrombosis, stroke and dementia.[42]

As an essential metabolic intermediate, homocysteine is involved in the transfer of activated methyl groups from tetrahydrofolate to S-adenosylmethionine, commonly referred to as the activated methyl cycle. It is also an intermediate in the synthesis of cysteine from methionine, by means of the transsulfuration pathway, and it may be activated to form homocysteinyl-tRNA, which potentially results in the production of homocysteine thiolactone, a highly reactive derivative. Homocysteine has one of three physiologically significant metabolic fates, it is either remethylated to methionine, or it may enter the cysteine biosynthetic pathway, or it is released into extracellular medium including urine and plasma.The last scenario is the least desirable, as it leads to increased concentrations of total homocysteine in extracellular fluids, including the urine and plasma.[41] The first scenario is catalyzed by methionine synthase, a folate-dependent reaction, which is catalyzed by the B12 dependent enzyme methionine synthase. Alternatively, homocysteine may be converted to cysteine via catalization by B6-dependent enzymes.[43]

Pantothenate - Pantothenic acid is not produced *in vivo*, and thus must be supplied in the diet. Pantothenic acid functions as a component of coenzyme A in fatty acid metabolism, providing the backbone for the SH groups of pathotheine, which in turn forms the reactive site.[25] It also functions as a cofactor in fatty acid synthesis as 4´-phosphopatetheine, which functions analogous to CoA during fatty acid oxidation, and is an integral part of the acyl carrier protein (ACP) molecule.[44] A significant correlation between mild pantothenate deficiency and triglyceride metabolism has been noted, demonstrating that pantothenate-deficiency was significantly correlated with elevated serum triglycerides and free fatty acids. Significant weight loss was also correlated to severe deficiency.[45] Additionally, pantothenate analogs, N-pentylpantothenamide and N-heptylpantothenamide have been indicated as pro-antiobiotics, shown to inhibit fatty acid synthesis and bacterial growth as a result of covalent modification of acyl carrier protein (ACP).[46]

Folic Acid - Due to its involvement in the metabolism of homocysteine, folic acid has been indicated as an independent risk factor in cardiovascular and thrombotic syndromes. Tissue and plasma concentrations of homocysteine are dependent upon folic acid, as well as vitamins B12 and B6, along with genetic factors. Hyperhomocysteinaemia is anticipated to be involved in approximately 10% of all cardiovascular risks,[47] and has been associated with vascular morphology alterations, including loss of endothelial anti-thromboitc function, and the initiation of a procoagulant atmosphere. A deficiency of folic acid is considered the most common cause of hyperhomocysteinemia.[48]

Factors That Support Energy Metabolism

Taurine - Taurine is a semi-essential amino acid derived from methionine. It is ubiquitous in mammalian tissues, and is the most abundant free amino acid in the heart, retina, skeletal muscle and leukocytes[49,50] Unlike most amino acids, is not incorporated into proteins, however, it acts in a regulatory mechanism via its role in maintaining the intracellular levels of sodium, potassium and magnesium. Cellular depletion of taurine has been linked to immunodeficiency, impaired cellular growth and the development of cardiomyopathy. Additionally, cardiovascular conditions, specifically congestive heart failure, have been designated to respond favorably to taurine supplementation. Taurine has also been implicated in minimizing the adverse effects of angiotensin II on Ca^{2+} transport, protein synthesis and angiotensin II signaling, thus minimizing the unfavorable effects of angiotensin II.[51] Consequently particular individuals may benefit from taurine supplementation, specifically those with chronic heart dysfunction, as well as hepatic or renal malfunction.[52]

L-Carnitine - Fatty acids are the primary oxidation fuel for the heart. The conversion of fatty acids to acyl-CoA in the cytoplasm, and subsequent transfer into the mitochondrial matrix is dependent upon the action of three carnitine dependent enzymes. These enzymes result in the production of acyl-CoA through the beta-oxidation pathway. Subsequently, the oxidation of carbohydrates may also result in the production of acetyl-CoA.[53]

L-Carnitine has been shown to reduce myocardial injury following myocardial reperfusion and ischemia via its ability to counteract the toxic effect incurred by high levels of free fatty acids occurring in ischemia, and by improving carbohydrate metabolism. The anti-ischemic properties of L-carnitine have been demonstrated clinically, indicating that the use of L-carnitine results in a reduction of ST segment depression on coronary angiograms and left ventricular end-diastolic pressure via Doppler echocardiography. An increase in tissue carnitine content of the myocardium was also noted following supplementation.[53,54] Additionally, there is considerable experimental evidence to suggest that L-carnitine exerts a protective effect in models of heart ischemia and hypertrophy, both *in vitro* and *in vivo*.[53]

Coenzyme Q10 - Ubiquionine or Coenzyme Q10 is an essential component of the mitochondrial respiratory chain, and functions, in a reversible manner, as both donors and acceptors of reducing equivalents from NAD, subsequently transferring electrons from flavoproteins to the cytochromes via cytochrome b5.[25] It plays a role in oxidative phosphorylation and has also shown membrane stabilizing properties. Additionally, its ability to quench free radicals is approximately fifty times greater than that of vitamin E, which supports the prevention of irreversible oxidative damage.[51] Given that Coenzyme Q10 is naturally produced *in vivo*, it is considered a conditionally essential nutrient. However, it may become an essential nutrient in certain circumstances, or with specific conditions, including cardiovascular disease and cofactor deficiencies, in addition to conditions that impose physiological stress on the body. In these instances biosynthesis may become inadequate to meet physiological needs, at which time it becomes an essential nutrient.[52]

Studies have indicated that coenzyme Q10 has properties beneficial to cardiovascular health, specifically addressing protection of the myocardium during cardiac surgery, end-stage heart failure, pediatric cardiomyopathy, and in cardiopulmonary resuscitation.[53] Additionally, in conjunction with other antioxidants, its capacity as an antioxidant is evidenced by means of its role in the prevention of LDL oxidation, and in the "oxidative lesion of endothelium", which arises as a result of increased expression of endothelial adhesion molecules, typical of the early stages of atherosclerosis.[54] Recently, atherosclerosis has also been correlated with the metabolic syndrome, with both disorders being classified as inflammatory conditions, indicating that coenzyme Q10 may also be beneficial in these circumstances.[55]

Deficiency may also result from the usage of prescription medications, given that a variety of drugs interfere with the *in vivo* production of coenzyme Q10. Thus it is critically important to provide an adequate supply of coenzyme Q10 for the myocardium to maintain energy production. The varieties of drugs that interfere with *in vivo* production of CoQ10 are diverse, but include cholesterol-lowering drugs, calcium channel blockers, psychotropic medications, and beta-blockers. Due to absorption inadequacies Biotics Research Corporation employs emulsified coenzyme Q10, which has been shown to support enhanced absorption.[56]

Additional Important Nutrients

Lysine and Methionine - These two amino acids are converted to carnitine *in vivo*. Furthermore, lysine is required as a component of connective tissue (collagen cross-linking), while methionine serves as a universal donor of methyl groups for neurotransmitters, phospholipids and other metabolites critical for the circulatory system.

Vitamin D - Vitamin D (1,25-(OH)2D3) supplementation has documented anti-inflammatory effects, and has also shown to be immunomodulating[57,58,59] A deficiency in vitamin D has been correlated with an increased risk of diseases, among which include cardiovascular disease, autoimmune disease, diabetes and rheumatoid arthritis.[60] In addition to its immunomodulating properties, vitamin D has also been correlated with anti-proliferative and differentiative activities.[60] In regard to cardiovascular conditions, vitamin D levels of less than 34 ng/mL (85 nmol/L) have been associated with a two-fold increase in the risk of heart attacks, as compared to those with vitamin D levels greater than indicated.[62]

Recent research suggests that higher levels of vitamin D provide protection from the conditions indicated above,[63] and were also inversely correlated with blood pressure.[64] Additionally, patients with congestive heart failure were been found to have markedly lower levels of vitamin D as compared to controls,[65] while vitamin D deficiency has been documented in numerous case reports of heart failure.[66-70]

Minerals

Magnesium - Magnesium is required as a cofactor in over 300 metabolic reactions, and is essential for the reduction of highly negatively charged molecules, including ATP. The consequences of magnesium deficiency have been shown to result in both elevated blood lipids, and in proliferation of smooth muscle cells, both of which are key elements in the atherogenic process.[25] Various studies have indicated the importance of magnesium in the pathogenesis of cardiovascular disease, encompassing hypertension and ischemic heart disease, particularly in high risk populations, including alcoholics, hypertensive patients or those with congestive heart failure.[71-73]

Additionally, low dietary consumption of magnesium has been correlated to an increased risk of cardiovascular disease, as well as an elevated level of C-reactive protein.[73] Supplementary magnesium plus folic acid has demonstrated beneficial cardiovascular effects, primarily due to its role in decreasing the production of homocysteine-inducing matrix metalloproteinase-2 (MMP-2) secretion, thus representing a beneficial position in the pathogenesis of coronary artery disease.[74]

Hypomagnesemia is correlated with other mineral imbalances as well, predominately sodium, potassium, and calcium.[75] Mechanistically, three distinct scenarios have been correlated with magnesium deficiency: an increased intracellular calcium concentration in cardiac myocytes, the formation of reactive oxygen species, and the production of inflammatory cytokines. Collectively, these may possibly result in the development of ischemic heart disease, congestive heart disease, sudden cardiac death, atherosclerosis, and arrhythmia.[71,76] Additionally, as a consequence of Mg deficiency, progressive vasoconstriction of the coronary vessels has been documented, which results in a reduction of the nutrient and oxygen delivery to cardiac myocytes.[77]

Calcium - In addition to its role as a structural element, calcium serves as an essential element in signal transduction, in which it acts as a second messenger for muscle contraction, release of neurotransmitters, and activation of glycogen breakdown. It also partakes in membrane transport, the release of neurotransmitters, the regulation of heartbeat, and the movement of ions through organelles like the mitochondria. Intracellular calcium (Ca^{2+}) has a documented role in the regulation of lipid metabolism and in triglyceride storage. Increased consumption has been correlated with the inhibition of lipogenesis, and the promotion of lipolyisis, lipid oxidation and thermogenesis, as well as inhibiting diet-induced obesity.[77] Adequate dietary calcium has been also been correlated with a reduced risk of hypertension.[78] In a study of adults aged 51 to 85 years, the consumption of calcium, along with other nutrients was determined to be lower than the estimated average requirements (EAR)[79] thus enforcing the need for an increase in dietary calcium. Additionally, calcium taken along with plant sterols appears to enhance their cholesterol- lowering effects.[80]

Potassium - As the major intracellular electrode, potassium is required for normal nerve transmission and muscle contraction. As a consequence of persistent severe potassium deficiency, termed hypokalemia, cardiac arrest incidences increase, due to the heart muscle's inability to contract. A significant inverse relationship has been documented between potassium intake and blood pressure (BP), in both hypertensive and nonhypertensive individuals, as confirmed by three meta-analyses, with high potassium intake associated with reduced BP.[81-83] Certain populations have shown enhanced benefits from dietary therapies, including increased potassium intake,[84] as established by scientific literature, which indicated that on average blacks have a higher prevalence of BP-related cardiovascular conditions than non-blacks.[85-87] Certain drugs, including diuretics, also have established potassium-depleting effects.

Trace Minerals

Copper - The essential nutritional value of copper has been documented in all species, and in humans copper is required as a cofactor in the function of many enzymes, including critical metabolic enzymes such as superoxide dismutase 1 (Cu/Zn-SOD), cytochrome *c* oxidase (COX) and tyrosinase.[88-92] Marginal deficits in copper have been implicated in contributing to an altered lipid metabolism, which results in elevated levels of serum cholesterol and triglycerides,[93] as well as to the development and progression of diabetes and cardiovascular disease.[94] Alterations in lipid metabolism, including elevated levels of plasma cholesterol, and triglycerides, along with a decrease in the whole-body respiratory quotient, have been correlated with copper deficiency.[95]

Lysyl oxidases (Lox) are extracellular copper enzymes that initiate the crosslinking of collagens and elastin. They serve an essential role in the cardiovascular system, as they are involved in both development and function. Lox inactivation has been shown to result in abnormalities in cardiovascular functions, as a result of structural alterations in the arterial walls. Additionally, it has been proposed that alterations in Lox activity may predispose individuals to cardiovascular diseases.[96] There has also been a correlation between copper deficiency and the hypotheses of ischemic heart disease. Associations between the two have designated similarities, as the pathophysiology, etiology and pathogenesis of ischemic heart disease has been deemed strikingly similar to copper deficiency, in contrast to other environmental insults.[97,98]

Chromium - The importance of dietary chromium is correlated to its role in insulin regulation, as well as to its effects on carbohydrate, protein and lipid metabolism. Insulin resistance is associated with the cluster of risk factors linked to cardiovascular disease.[99,100] Chromium supplementation has been implicated in reducing the risk of a first myocardial infarction, particularly in males, as this risk was inversely correlated with low chromium concentrations.[101] Individuals diagnosed with type 2 diabetes are at a higher risk of having low levels of blood chromium, as compared to non-diabetics. Supplemental chromium proved beneficial in these individuals, as adequate chromium nutrition was linked to a decreased insulin requirement, and an improved blood lipid profile.[102] In separate population groups, individuals diagnosed with the metabolic syndrome, affecting 40% of persons aged 60 to 70, or with insulin resistance, the development of cardiovascular disease is significantly increased. These groups are considered high-risk categories; as these syndromes have shown to significantly increase the risk of cardiovascular disease. Studies in these groups indicate that blood levels of chromium are decreased, as compared to healthy individuals,[99] proposing a beneficial effect of added dietary chromium. A recent study implicated that in patients with hypercholesterolemia and type-2 diabetes mellitus, a combination of chromium plus biotin resulted in significant decreases in both total cholesterol and low-density lipoprotein cholesterol (LDL-C) ($P<0.05$). The authors concluded that "intervention with chromium plus biotin resulted in improvement in "cardiometabolic risk factors."[103]

Zinc - Zinc is an essential component in many key enzymes, including DNA and RNA polymerases, alkaline phosphatase and superoxide dismutase, via its role as a cofactor. In addition to this role, it also serves in roles constituting both structural (zinc-fingers) and regulatory.[104] The zinc hypothesis of aging postulates that over time a gradual deficiency in zinc occurs in every living cell, resulting in less availability of zinc for the metalloenzymes. Adequate zinc status has been correlated with enhanced immunity, specifically in the aging, as a low bioavailability of zinc has been associated with a low immunoresistance to infection. Zinc supplementation was shown to restore the immune response, in addition to prolonging survival.[106]

Additionally, dietary zinc has demonstrated an inverse relationship with cardiovascular disease mortality, as a higher intake of zinc has been correlated with a reduction in CVD mortality, particularly in the presence of a disrupted iron homeostasis, which may be triggered by alcohol consumption.[107]

Vanadium - Vanadium is an ultratrace mineral naturally occurring in foods at various concentrations. Higher levels of vanadium are commonly found in leafy vegetables and mushrooms, while foods of animal origin and those rich in starch and sugar are poor sources of vanadium. Initial studies on the action of vanadium were associated with the support of normal blood sugar and the maintenance of cardiac performance in diabetic animals.[108] Within the past ten years, experimental evidence and clinical research has contributed to the understanding of the potent insulin-mimetic and cardiovascular protective action of vanadium.[109] Along with diabetes, insulin resistance has been correlated to hypertension and cardiovascular disease. [110] An inverse relationship between insulin action and vanadium levels has been recognized, with supplementation being linked to the management of insulin resistance.[111-113] One study conducted by A.B. Goldfine, *et. al.* demonstrated vanadium's potent hypoglycemic action in patients with both insulin-dependent (IDDM), and noninsuiln dependent (NIDDM) diabetes mellitus. The study established a significant glucose improvement in NIDDM patients, in addition to a beneficial result in the IDDM group, as evidenced by a significant decrease in insulin requirement. In both groups a significant decreased in cholesterol levels {IDDM, $P = 0.06$ and NIDDM, $P < 0.05$} was noted.[114] In a second study, aimed at assessing the effects of vanadium on cardiac performance and energy metabolism, supplemental vanadium was shown to restore the production of high-energy phosphates by the myocardium, as well as improve the metabolic process via regulation of myocardial dysfunction by regulating metabolic processes. Moreover, in rodent models of diabetes, vanadium was correlated with improvements in abnormalities of gene expression involved in carbohydrate and lipid metabolism, and was shown to enhance glucose transport, and glycogen and lipid synthesis, as well as to inhibit gluconeogenesis and lipolysis in isolated cells.[116]

Boron - Like vanadium, boron is also classified as an ultratrace element. Boron is naturally occurring in foods such as non-citrus fruits, including plums, apples, pears, and avocados, in legumes and nuts as well as in coffee and red wine.[117] Dietary boron exerts influence on the activity of many metabolic enzymes, along with the metabolism of steroid hormones and several micronutrients, including calcium, magnesium, and vitamin D. Human studies have suggested that boron is an essential mineral in calcium metabolism, brain function, energy metabolism, and perhaps immune processes, as indicated by its favorable effect on these processes.[118] In animal models boron supplementation has been shown to increase bone strength, and has been suggested as a participant in improving plasma lipid profiles as well as arthritis [119,120] Boron supplementation has also been correlated with the elevation of endogenous estrogen, suggesting a protective role in atherosclerosis.[121]

Selenium - As a component of the selenoproteins, selenium is utilized by most cell types and has an established essentiality as a dietary element. As a cofactor selenium has a documented role for glutathione peroxidase, viewed as one of the major antioxidant enzymes of the myocardium.[122] Epidemiological data has correlated selenium deficiency with an increased risk of cardiovascular and neurodegenerative disorders.[123] Selenium deficiency has also been associated with an increased susceptibility to both oxidative stress[124] and toxicity effects due to mercury.[125,126] Additionally, an insufficiency in selenium was associated with altered activities of biotransformation enzymes, which are enzymes involved in the metabolism and elimination of a variety of both exogenous (drugs, toxins and carcinogens) and endogenous compounds (steroid hormones), specifically glutathione S-transferase activity.[127]

In studies assessing cardiovascular protection, a beneficial role for dietary selenium, was demonstrated, which was predominantly due to its ability to prevent ischemia-reperfusion (I/R)-induced injury. In I/R hearts selenium's protective effect was attributed to its action on the redox state, as well as to the deactivation of NF-kappaB.[128] Mechanistically, selenium deficiency was shown to impair the recovery from ischemia-reperfusion via down-regulation of the activity of thioredoxin reductase (Txnrd) and glutathione peroxidase (Gpx), while with the addition of selenium an increase the endogenous activity of these enzymes was demonstrated, resulting in improved cardiac recovery from post ischemia reperfusion,[124] thus implicating an important role for selenium in cardiovascular health. Selenium supplementation was also shown to modulate the levels of protein carbonyls and lipid peroxides, resulting lower levels of these compounds, subsequently improving cardiac function post ischemia-reperfusion.[129] The latest studies on selenium have correlated supplementation to the downregulation of the enzymatic expression of apoB and HMG-CoA reductase, both known to be involved in hyperlipidemia, which resulted in a therapeutic benefit on lipid metabolism.[130] Selenium supplementation was associated with protection against free radical damage, specifically against damage to the myocardium by the superoxide radical, via its ability to improve glutathione peroxidase mRNA expression.[131]

Rubidium - In animal studies, rubidium-deficient diets have been correlated with an altered tissue distribution of trace nutrients including sodium, potassium, phosphorus, calcium, magnesium, iron, zinc and copper.[132] Additionally, Rubidium has been studied as a component of the Na^+/K^+-ATPase[133,134] whereby it was demonstrated that in addition to other trace elements, it exhibits the capability to replace K as a component of the dephosphorylation reaction.[135]

Botanical Support of the Cardiovascular System

Hawthorn Berries (*Crataegus oxyacantha*) - The cardiac benefits of Hawthorn extracts have been primarily attributed to its bioflavonoid-like complexes; include vitexin, quercetin, hyperoside, proanthocyanidins, and other oligomeric procyanidins (OPCs), which are found in the leaves, flowers and berries.[136] In a meta-analysis of randomized, double-blind, placebo controlled trials, focusing on the use of Hawthorn extract for cardiovascular issues, the authors concluded that, when incorporated into the treatment program, hawthorn extract had a significant benefit, as compared to placebo, which was evidenced by a favorable decrease in the ventricle pressure-heart rate product (systolic BP in mm Hg X heart rate/minute ÷ 100). In addition, common negative symptomatology, including fatigue and dyspnea, was significantly improved in the Hawthorne group, as compared to placebo.[137] In left ventricle systolic dysfunction Hawthorn administration has also shown a favorable effect on the contractility of the weakened myocardium.[138] Other studies have indicated improved symptomatology when utilizing Hawthorn for the treatment of patients categorized by the NYHA II classification of congestive heart failure.[139-142] Crataegus extract has also shown hepatoprotective effects on liver abnormalities induced as a consequence of myocardial infarction.[143]

Octacosanol - Is a mixture of long-chain waxy alcohols, the main component being policosanol. Animal studies incorporating supplemental octacosanol have shown an increased ability to perform physical exercise, as a result of an increased work capacity of the muscle.[144] This was correlated with a substantial increase in muscle octacosanol storage in response to exercise, which was hypothesized to result as a consequence of an increased mobilization of free fatty acids from fat cells within the muscle. Octacosanol supplementation was also shown to increase running endurance times, while simultaneously sparing muscle glycogen stores, and increasing muscle oxidative capacity. Supplementation was also shown to significantly increase plasma creatine phosphokinase activity, (44% increase, $P<0.01$),[145] as well as muscle citrate synthase activity (16%, $P<0.01$). In vertebrates the enzyme creatinine phosphokinase maintains a high concentration of ATP during periods of muscular exertion, while citrate synthase is an integral part of the citric acid cycle, catalyzing the conversion of oxaloacetate to citrate, which in turn is catalyzed to CoA.[146]

Policosanol - The primary component of octacosanol, has shown affirmative results in lowering total cholesterol, LDL cholesterol, LDL-cholesterol/HDL cholesterol ratio, and total cholesterol/HDL cholesterol ratio, while increasing HDL cholesterol, making it a beneficial component for cardiovascular support. Triglycerides have also responded favorably to policosanol supplementation, being lowered significantly with supplementation.[147]

Additional Nutritional Components for Cardiovascular Support

Glandular Support - The circulatory and endocrine systems are in delicate balance, as the hormones produced by the endocrine system are secreted directly into the circulatory system. These hormones in turn serve to regulate, influence and control many bodily processes, where they serve to trigger biological effects. Subsequently, the health of the endocrine system relies upon specific nutritional support. The neonatal tissues supplied in Biotics Research Corporation's products have been shown to possess very active glands and tissues, demonstrating high anabolic activity. Factors associated with rapid growth are more likely to be present in neonatal tissues as opposed to adult tissues. Additionally, neonatal tissues have not been subjected to lifelong exposure to pollutants and environmental stressors. An independent evaluation of common pesticides in neonatal glandulars indicated that pesticide levels were below the limits of detection, while histological evaluation of adult (2–5 years old) bovine glands and neonatal (newborn) bovine glands dramatically illustrated the differences, likely due to aging and environmental exposure.[148] These very effects contribute to a loss of organ function, accumulation of lipofusion and/or increased fat deposition.

Neonatal adrenal glands reveal three distinct cortical zones. These zones are much less distinct in the adult bovine gland. In addition, the zona glomerulus of adult cortex exhibited a large amount of lipofuscin, indicating cumulative free radical damage. These deposits were absent from neonatal bovine tissues. All glandular supplements produced by Biotics Research Corporation are obtained from domestic, USDA approved animals.

Purified Chondroitin Sulfates - Although primarily utilized for musculoskeletal support, purified chondroitin sulfate has also shown cardioprotective attributes, and offers a secondary preventative measure in cardiovascular support. Purified chondroitin sulfate has been shown to promote normal function of the circulatory system,[149,150] and human studies indicate that orally consumed chondroitin sulfates are efficiently absorption. Studies utilizing human fibroblast cultures have demonstrated the antioxidant-like properties of glycosaminoglycans (GAGs), the class of compounds of which chondroitin sulfates belong. This was exhibited by a reduction in cell death, an inhibition of lipid peroxidation, and a decrease in hydroxyl radical (OH-) generation. They were also shown to limit oxidative damage, evidenced by limited DNA fragmentation and protein oxidation.[152] In a separate study chondroitin sulfate was shown to inhibit the nuclear translocation of NF-kB, and to reduce IL-1b. The authors concluded in stating "these results suggest that some of the biological activities of chondroitin sulfate may be associated to the reduction in Erk1/2 and p38MAPK phosphorylation and nuclear transactivation of NF-kB."[153] Other studies have verified chondroitin sulfate's antioxidant capacity, by virtue of its ability to reduce molecular damage due to free radicals and other associated oxygen reactants.[154,155]

Essential Fatty Acids

Essential fatty acids in general are important for cardiovascular health. Furthermore, both deficiencies and imbalances in fatty acids are common, especially in industrialized societies. Lower cardiovascular risk has been linked with the consumption of both omega-6 and omega-3 polyunsaturated fatty acids.[156] **Bio-Cardio Packs®** contains flax seed oil, a source of essential fatty acids intended for comprehensive cardiovascular support.

Omega-3 Fatty Acids

Flax Seed Oil (ALA) - Flax seed oil has demonstrated effectiveness in cardiovascular health, as evidenced by its ability to suppress accelerated rhythms of the heart,[157] and to slow platelet aggregation. In the Nurses' Health Study, a higher intake of ALA was associated with a lower risk of fatal ischemic heart complications.[158] This association has also been observed in males, with an intake of linolenic acid inversely associated with the risk of myocardial infarction.[159] An increase in dietary ALA has also been correlated to a reduced risk of sudden cardiac death (SCD) in women, which is extremely significant given the fact that most women having cardiovascular complications resulting in sudden death do not have a history of cardiovascular disease.[160] In regards to repression of accelerated heart rhythms, ALA was shown to act directly on voltage-gated potassium channels (Kv1.5 atria-specific channels), serving to block them without modifying their expression, thus demonstrating a direct effect by ALA on cardiac ion channels.[161] Although humans can convert ALA to EPA and DHA, the conversion is extremely inefficient, estimated at 5% conversion to EPA and <0.5% conversion to DHA.[162] ALA has also demonstrated effectiveness in lowering markers of inflammation.[163] The Flax seed in Biotics Research Corporation's products is certified organic.

Fish Oil (EPA and DHA) - In populations consuming a high quantity of fish, such as the Eskimo or Japanese populations, a lower risk of cardiovascular complications has been observed,[164] and a reduction in the all-cause mortality risk for both ischemic heart complications and stroke has been correlated to a high fish intake.[165] Even modest intake (250-500 mg/day of EPA and DHA) has been associated with a lower risk (≥25%) of cardiovascular complications, compared to no intake at all. In taking together both randomized trials and placebo-controlled, double-blind, randomized trials, marine omega-3 polyunsaturated fatty acids were shown to reduce total mortality by 17%, which is comparable in effectiveness to HMG CoA-Reductase inhibitors, which reduced total mortality by 15%.[166] A decrease in the production of inflammatory cytokines and eicosanoids resulting from the intake of long-chain n-3 fatty acids from fish oil has been demonstrated,[167] primarily due to the shift in eicosanoid production to a less inflammatory mixture.[168] Consequently, fish oil consumption has demonstrated anti-inflammatory benefits, as evidenced by its ability to suppress the production of both TNF-α and IL-1β or both in healthy subjects,[169-171] as well as in patients with rheumatoid conditions. Aside from these benefits a greater intake quantity of EPA and DHA was correlated to a lower intake of saturated fat, monounsaturated and trans fatty acids.[173] Due to the concerns of heavy metal exposure, the use of quality fish oil is pertinent.

Combination Fatty Acids – The use of combination fatty acids has beneficial results due to several factors. Foremost, fatty acid deficiencies typically occur in combination, thus the use of a combination fatty acid serves to ameliorate this deficiency. Additionally, it is well known that fatty acids compete for cell membrane space, thus supplementation with only one essential fatty acid may exacerbate this deficiency.[174] Essential fatty acids used in combination have demonstrated beneficial results for the prevention of sudden cardiac death, indicating a lower risk with a higher intake of a combination of fatty acids (ALA, DHA & EPA).[160] In a separate study, healthy women were shown to have a favorable alteration in both lipid and fatty acid profiles with EPA + DHA + GLA supplementation.[175]

Combined nutritional deficiencies are known to contribute to cardiovascular complications, thus a comprehensive approach is to cardiovascular health is relevant. Nutritional supplementation with cardio-supportive ingredients serves to complement lifestyle improvements and dietary changes. Studies have implicated that cardiovascular complications are largely preventable given proper intervention.[176]

Supplement Facts

Serving Size: 4 Capsules
Servings Per Container: 30

	Amount Per Serving	% Daily Value
Vitamin A (as natural mixed carotenoids and acetate) (IU ratio 1:1)	1,590 mcg RAE	177%
Vitamin C (as magnesium and calcium ascorbate)	120 mg	133%
Vitamin D (as cholecalciferol)	5 mcg	25%
Vitamin E (as d-alpha tocopheryl acetate)	20 mg	133%
Vitamin K (as phytonadione)	10 mcg	8%
Thiamin B1 (cocarboxylase chloride)	2 mg	167%
Riboflavin (B2) (as riboflavin-5-phosphate)	2.3 mg	177%
Niacin (as niacinamide and niacin)	20 mg	125%
Vitamin B6 (as pyridoxal-5-phosphate)	15 mg	882%
Folate (as calcium folinate)	400 mcg DFE	100%
Vitamin B12 (as methylcobalamin)	30 mcg	1,250%
Biotin	300 mcg	1,000%
Pantothenic Acid (as calcium pantothenate)	10 mg	200%
Calcium (as calcium citrate)	60 mg	5%
Magnesium (as citrate, glycinate and ascorbate)	120 mg	29%
Zinc (as zinc gluconate)	5 mg	45%
Selenium (from vegetable culture †)	50 mcg	91%
Copper (as copper gluconate)	1 mg	111%
Manganese (as manganese gluconate)	2 mg	87%
Chromium (from vegetable culture †)	50 mcg	143%
Potassium (as potassium chloride)	99 mg	2%

Taurine 200 mg*, L-Carnitine fumarate 30 mg*, L-Methionine 25 mg*, L-Lysine hydrochloride 25 mg*, L-Cysteine HCl 10 mg*, Neonatal Heart (bovine) 100 mg*, Lamb Pituitary / Hypothalamus complex (ovine) 10 mg*, Adrenal Complex Concentrate†† 10 mg*, Neonatal Pancreas (bovine) 10 mg*, Hawthorne (berry) 50 mg*, Vanadium (from vegetable culture †) 5 mcg*, Octacosanol (from rice) 500 mcg*, Coenzyme Q10 (emulsified) 1 mg*, Superoxide dismutase (from vegetable culture †) 20 mcg*, Catalase (from vegetable culture †) 20 mcg*

*** Daily Value not established**

Other ingredients: Capsule shell (gelatin and water), cellulose, stearic acid and magnesium stearate (vegetable source).

† Specially grown, biologically active vegetable culture (from organic peas, lentils, and/or chickpeas) containing **Phytochemically Bound Trace Elements™** and/or naturally associated phytochemicals including polyphenolic compounds with SOD and catalase, dehydrated at low temperature to preserve associated enzyme factors.

†† A unique proprietary complex of neonatal bovine tissue and porcine tissue concentrates.

This product is gluten and dairy free.

RECOMMENDATION: Four (4) capsules each day as a dietary supplement or as otherwise directed by a healthcare professional.

Bio-Cardiozyme Forte® is available in
120-count and 360-count bottles (#2900 - #2901).

Supplement Facts

Serving Size: 1 packet

	Amount Per Serving	% Daily Value
Calories	20	
Calories from Fat	20	
Total Fat	2 g	3%†
Saturated Fat	0 g	0%†
Cholesterol	0 mg	0%
Vitamin A (as natural mixed carotenoids and acetate) (IU ratio 1:1)	1,460 mcg RAE	162%
Vitamin C (as ascorbic acid and magnesium ascorbate)	200 mg	222%
Vitamin D (as cholecalciferol)	20 mcg	100%
Vitamin E (as d-alpha tocopheryl acetate) (emulsified)	268 mg	1,787%
Vitamin K1 / K2 (as phytonadione, menaquinone-7)	120 mcg	100%
Thiamin (B1) (as cocarboxylase chloride)	3 mg	250%
Riboflavin (as riboflavin-5-phosphate)	4 mg	308%
Niacin (as niacinamide)	100 mg	625%
Vitamin B6 (as pyridoxal-5-phosphate)	8 mg	471%
Folate (as calcium folinate)	800 mcg	200%
Vitamin B12 (as methylcobalamin)	17 mcg	708%
Biotin	300 mcg	1,000%
Pantothenic Acid (as calcium pantothenate)	12 mg	240%
Calcium (as calcium citrate)	100 mg	8%
Iodine (from kelp and potassium iodide)	100 mcg	67%
Magnesium (as magnesium glycinate and magnesium ascorbate)	100 mg	24%
Zinc (as zinc gluconate)	15 mg	136%
Selenium (from vegetable culture ††)	50 mcg	91%
Copper (as copper gluconate)	2 mg	222%
Manganese (as manganese gluconate)	2 mg	87%
Chromium (from vegetable culture ††)	50 mcg	143%
Potassium (as potassium chloride)	99 mg	2%
Boron (as calcium borogluconate)	1 mg	*
Rubidium (from vegetable culture ††)	20 mcg	*
Vanadium (from vegetable culture ††)	10 mcg	*
Coenzyme Q10 (emulsified)	50 mg	*
L-Cysteine HCl	50 mg	*
L-Methionine	100 mg	*
Taurine	150 mg	*
Omega-3 fatty acids (from 2 g fish oil providing not less than 800 mg EPA & 600 mg DHA)	1,600 mg	*
Superoxide Dismutase (from vegetable culture ††)	30 mcg	*
Catalase (from vegetable culture ††)	30 mcg	*

† Percent Daily Value based on a 2,000 calorie diet.
*** Daily Value not established**

Other ingredients: Capsule shell (gelatin, glycerin and water), magnesium stearate (vegetable source), and gum arabic.

Contains ingredients derived from Anchovy.

†† Specially grown, biologically active vegetable culture (from organic peas, lentils, and/or chickpeas) containing **Phytochemically Bound Trace Elements™** and/or naturally associated phytochemicals including polyphenolic compounds with SOD and catalase, dehydrated at low temperature to preserve associated enzyme factors.

This product is gluten and dairy free.

RECOMMENDATION: One (1) packet each day as a dietary supplement or as otherwise directed by a healthcare professional.

CAUTION: Not recommended for pregnant women.

Bio-Cardio Packs® is available in
30-count bottles (#2910).

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