Review

Nutrition, physical activity, and cardiovascular disease: An update

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Abstract

Many epidemiological studies have indicated a protective role for a diet rich in fruits and vegetables against the development and progression of cardiovascular disease (CVD), one of the leading causes of morbidity and mortality worldwide. Physical inactivity and unhealthy eating contribute to these conditions. This article assesses the scientific rationale of benefits of physical activity and good nutrition on CVD, especially on atherosclerosis-related diseases. Compelling evidence has accumulated on the role of oxidative stress in endothelial dysfunction and in the pathogenesis of CVD. Reduced nitric oxide (NO) bioavailability due to oxidative stress seems to be the common molecular disorder comprising stable atherosclerotic narrowing lesions. Energy expenditure of about 1000 kcal (4200 kJ) per week (equivalent to walking 1 h 5 d a y s w e e k ) is associated with significant health benefits. Such benefits can be achieved through structured or nonstructured physical activity, accumulated throughout the day (even through short 10-min bouts) on most days of the week. Some prospective studies showed a direct inverse association between fruit and vegetable intake and the development of CVD incidents such as acute plaque rupture causing unstable angina or myocardial infarction and stroke. Many nutrients and phytochemicals in fruits and vegetables, including fiber, potassium, and folate, could be independently or jointly responsible for the apparent reduction in CVD risk. Novel findings and critical appraisal regarding antioxidants, dietary fibers, omega-3 polyunsaturated fatty acids (n-3 PUFAs), nutraceuticals, vitamins, and minerals, are presented here in support of the current dietary habits together with physical exercise recommendations for prevention and treatment of CVD.

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Keywords: Nutrition; Physical activity; Cardiovascular disease

1. Introduction

To date cardiovascular disease (CVD) remains one of the leading causes of morbidity and mortality worldwide. Although genetic factors and age are important in determining the risk, other factors, including hypertension, hypercholesterolemia, insulin resistance, diabetes, and lifestyle factors such as smoking and diet are also major risk factors associated with the disease [1]. The emphasis so far has been on the relationship between serum cholesterol levels and the risk of coronary heart disease (CHD) [1,2]. Indeed, experimental, clinical, and epidemiologic data capped by stunning Interventional results with the statins has established hypercholesterolemia as a major causative factor in atherogenesis. It is equally clear that from the very beginning atherogenesis has a strong inflammatory component, e. g., it is characterized by penetration of monocytes and of T-cells into the developing lesion. But inflammation has to occur in response to something. What is that something? The case will be made that oxidized lipids generated in response to prooxidative changes in the cells of the artery wall should be considered a plausible candidate (see below). Thus, there is no need to consider hypercholesterolemia and inflammation as alternative hypotheses. Both are very much involved.

In this update, we examine the scientific evidence in support of both dietary and physical activity recommendations for CVD...
There is a considerable weight of already published articles elsewhere on this topic, thus, we decided to provide only the novel findings and scientific trends coming in the latest years. One problem is that it is very difficult to assess prospectively the causal relationship of nutrition/physical exercise on major cardiovascular events. This is because the natural history of such disease is often extremely long. Available evidence indicates that persons who consume more fruits and vegetables often have lower prevalence of important risk factors for CVD, including hypertension, obesity, and type 2 diabetes mellitus. Some large, prospective studies showed a direct inverse association between fruit and vegetable intake and the development of CVD incidents such as CHD and stroke. However, the biologic mechanisms whereby fruits and vegetables may exert their effects are not entirely clear and are likely to be multiple. Many nutrients and phytochemicals in fruits and vegetables, including fiber, potassium, and folate, could be independently or jointly responsible for the apparent reduction in CVD risk [3,4]. Functional aspects of fruits and vegetables, such as their low dietary glyceric load and energy density, may also play a pivotal role.

There is a plethora of experimental and clinical studies supporting the evidence that moderate exercise is a deterrent of CVD and atherosclerosis [5–9]. We provided clear evidence for the beneficial effects of graduated physical training (swimming) and metabolic treatment (antioxidants and L-arginine) on atherosclerotic lesion formation in hypercholesterolemic mice [10]. These protective mechanisms could include increased antioxidant defenses and NO bioactivity, reduced basal production of oxidants (reduced oxidative stress), and reduction of radical leak during oxidative phosphorylation [10–14]. Basically, early oxidation-sensitive mechanisms are associated with early stages of human atherogenesis [14–16].

Another study [17] also provided direct evidence that inactivity enhances vascular oxygen radical production, endothelial dysfunction and atherosclerosis in hypercholesterolemic mice. Thus, graduated exercise training can increase NO bioavailability and convey benefit in vasculoprotection [10,18,19]. NO so generated may even scavenge overwhelming radicals, such as superoxide anion, thereby preventing tissue damage. In contrast, prolonged strenuous exercise and high blood pressure reduce the cyclic pulsations (physiological shear stress), thereby limiting NO production [18,19]. NO bioavailability can be restored by antioxidants and L-arginine, the natural precursor of NO. Several small-scale studies have demonstrated that intravenous L-arginine augments endothelial function and improves exercise ability in patients with CVD by enhancing vasodilation and reducing monocytic adhesion [20] reviewed in [21]. L-arginine normalizes aerobic capacity [22] and reduces fat mass in Zucker diabetic fatty rats [23]. The lack of appropriate generation of endogenous NO is an important progression factor of atherosclerosis in mice [24] and L-arginine may reduce atherogenesis in hypercholesterolemic mice [25]. Thus, there is convincing evidence that moderate physical exercise, antioxidants and L-arginine have beneficial effects on atherosclerotic lesions.

Clinical studies have shown that severe physical exercise can lead to the generation of more free radicals than the endogenous antioxidant systems can scavenge, whereas moderate intensity aerobic exercise improves endothelial function and reduces cardiovascular risk [12,13]. Several highly plausible protective mechanisms have been postulated, including decreased myocardial oxygen demand, increased myocardial oxygen supply, reduced propensity toward ventricular arrhythmias, reduced platelet aggregation, improved lipid profile, and increased plasma fibrinolytic activity [12,13]. Despite the substantial body of literature, pathogenic mechanisms at the cellular and molecular level by which exercise might benefit vascular diseases are poorly understood. However, it is conceivable that arterial cells can be affected by multiple signal transduction events promoted by early graduated physical exercise. Short-term oral administration of L-arginine improved hemodynamics and exercise capacity in patients with precapillary pulmonary hypertension [26], and enhanced myocardial perfusion in CHD patients [27–32]. In addition, oral L-arginine supplementation enhanced the beneficial effect of exercise training on endothelial dysfunction in patients with chronic heart failure [33]. From these points of view and mixed background, we will try to update this field which is in continuous renewal.

2. Oxidative stress, L-arginine and nutritional aspects

Oxidative stress induced by reactive oxygen species (ROS and other radical species) is considered to play an important part in the pathogenesis of several diseases, including CHD, stroke, cancer, shock and aging [34–39]. Oxidation of the circulating low-density lipoprotein (LDL) that carry cholesterol into the blood stream to oxidized LDL (LDLox) is thought to play a pathogenic role in atherosclerosis, which is the underlying disorder leading to heart attack and ischemic stroke [1,2,37,40]. More importantly, during human fetal development [15] and early infancy [16] there is evidence of LDLox in early atherosclerotic lesions. Overall, a very complex interaction between maternal cholesterolemia and fetal circulation occurs during pregnancy (reviewed in [41] and [42]). Thus, antioxidant nutrients are believed to slow the progression of atherosclerosis because of their ability to inhibit the damaging oxidative processes [37,40,41,43]. The “fetal origins” hypothesis of atherogenesis postulates that conditions, most likely nutritional and genetics, “program” the fetus for the development of advanced forms of the CVD and CHD in adulthood [41,44]. It remains to be established whether these associations are causal. The role of birth weight remains difficult to interpret except as a proxy for events in intrauterine life. Unfortunately, birth weight does not make an important contribution to the population attributable risk of CVD; lifestyle factors during adulthood make much greater contributions.

A number of antioxidants showed beneficial effect in experimental models of atherosclerosis and CHD [1,2,35,37,38,40,41,43]. Fig. 1 elucidates the cascade of oxidation-
sensitive events and NO generation [45] in relation to some antioxidant intervention. Recently, the combination of vitamin E and C and L-arginine, the natural precursor of nitric oxide, provided convincing beneficial effects in perturbed shear stress-induced atherosclerosis [20,46] and by enhancing the protection afforded by moderate physical exercise [10]. LDLox may induce a decreased uptake of L-arginine [47]. The local depletion of the L-arginine substrate may derange the endothelial nitric oxide synthase (eNOS), leading to overproduction of superoxide radical from oxygen, the co-substrate of eNOS. Interestingly, glycoxidized LDL downregulates eNOS in human coronary cells [48]. Several epidemiological and prospective studies have shown that consumption of antioxidant vitamins such as vitamin E and β-carotene may reduce the risk of CHD [37,49,50]. Some randomized clinical trials also suggest a reduced risk of CHD with vitamin E supplementation [43,51–53]. However, some large-scale human trials have failed to confirm the protective effect of L-arginine or β-carotene and have produced inconclusive results with vitamin E.

In the recently completed Heart Outcomes Prevention Evaluation (HOPE) Study [54,55] or in the Heart Protection Study [56], supplementation with vitamin E did not result in any beneficial effects on cardiovascular events. Another randomized clinical trial on Vascular Interaction With Age in Myocardial Infarction (VINTAGE MI) L-arginine, when added to standard postinfarction therapies, does not improve vascular stiffness measurements or ejection fraction and may be associated with higher postinfarction mortality [57]. Moreover, also supplements combining folic acid and vitamins B6 and B12 did not reduce the risk of major cardiovascular events in patients with vascular disease [58]. More likely, antioxidant intervention may affect long-term lesion progression but not necessarily modulate the properties of preexisting advanced atherosclerotic lesions (i.e., CHD, cerebrovascular disease, and peripheral arterial disease) or reduce the clinical manifestations of plaque rupture [37]. Thus, to test whether antioxidants inhibit atherosclerosis it is necessary to investigate the progression of early atherosclerotic lesions in young adults. In addition, such intervention may prevent proatherogenic programming events during fetal development [41].

3. Emerging nutritional aspects and CVD

3.1. Lycopene

Lycopene, a naturally present carotenoid in tomatoes and tomato products, is one such dietary antioxidant that has received much attention recently [59,60]. Epidemiological studies have shown an inverse relationship between the intake of tomatoes and lycopene and serum and adipose tissue lycopene levels and the incidence of CHD [61–64]. A number of in vitro studies have shown that lycopene can protect native LDL from oxidation and can suppress cholesterol synthesis [65,66]. However, dietary enrichment of endothelial cells with β-carotene but not lycopene inhibited the oxidation of LDL [67]. One of the earlier studies that investigated the relationship between serum antioxidant status,
including lycopene and myocardial infarctions [68], reported
an odd ratio of 0.75. The strongest population-based
evidence from a recently reported multicenter case-control
study (EURAMIC) [61] indicated that only lycopene, and
not β-carotene, levels were found to be protective with an
odd ratio of 0.52 for the contrast of the 10th and 90th
percentiles with a P value of 0.005. A component of this
larger EUREMIC study representing the Malaga region was
analyzed further [69]. In this case-control study adipose
tissue lycopene levels showed an odd ratio of 0.39. In another
Atherosclerosis Risk in Communities (ARIC) case-control
study, an odd ratio of 0.81 was observed when fasting serum
antioxidant levels of 231 cases and an equal number of
control subjects were assessed in relationship to the intima-
media thickness [70]. In a cross-sectional study comparing
Lithuanian and Swedish populations showing diverging
mortality rates from CHD, lower blood lycopene levels
were found to be associated with increased risk and mortality
from CHD [71]. In the Austrian stroke prevention study, lower
levels of serum lycopene and α-tocopherol were
reported in individuals from an elderly population at high risk
for cerebral damage [72]. Although the epidemiological
studies conducted so far provide convincing evidence for
the role of lycopene in CHD prevention, it is at best only sug-
gestive and not proof of a causal relationship between ly-
copene intake and the risk of CHD. Such a proof can be
obtained only by performing controlled clinical dietary in-
tervention studies where both the biomarkers of the status of
oxidative stress and the disease are measured.

There is a need related to the identification of genetic
determinants or biomarkers that predict which individuals
are at highest risk for chronic heart failure (CHF). In dietary
intervention studies healthy human subjects, nonsmokers,
and not on any medication and vitamin supplements, con-
sumed lycopene (20 to 150 mg per day) from traditional
tomato products and nutritional supplement for 1 week re-
sulting in a significant increase in serum lycopene levels and
lower levels of serum lipid peroxidation, LDL cholesterol
protein, and DNA oxidation [73–75]. Fig. 1 suggests the
general role of antioxidant lycopene in the disruption of
oxidation-sensitive events. Long-term studies, the use of
well-defined subject populations, standardized outcome
measures of oxidative stress and the disease, and lycopene
ingestion are essential for a meaningful interpretation of the
results. Circulating and adipose tissue levels of lycopene
seem to be better indicators of disease prevention than die-
tary intake data. Moreover, we still underscore the fact that a
better understanding of how genes and gene–environment
interaction lead to the CVD is crucial together with a better
focusing of ethnic/racial differences in the development and
progression of CVD.

3.2. Polyphenols contained in the pomegranate fruit

Polyphenols are the most abundant antioxidants in the
diet. Their main dietary sources are fruits and plant-derived
beverages such as fruit juices, tea, coffee, red wine, cereals,
chocolate, and dry legumes. Their total dietary intake could
be as high as 1 g/d, which is much higher than that of all
other classes of phytochemicals and known dietary anti-
oxidants. For perspective, this is ∼10 times higher than the
intake of vitamin C and 100 times higher that the intakes of
vitamin E and carotenoids [76,77]. Despite their wide dis-
tribution in plants, the health effects of dietary polyphenols
have come to the attention of nutritionists only rather re-
cently [78]. For many years, polyphenols and other anti-
oxidants were thought to protect cell constituents against
oxidative damage through scavenging of free radicals. How-
ever, this concept now appears to be an oversimplified view
of their mode of action. More likely, cells respond to poly-
phenols mainly through direct interactions with receptors or
enzymes involved in signal transduction, which may result in
modification of the redox status of the cell and may trigger a
series of redox-dependent reactions [76,77,79]. Evidence for
a reduction of disease risk by flavonoids was considered
“possible” for CVD and “insufficient” for cancers in a recent
report from the World Health Organization [80]. Much of the
evidence on the prevention of diseases by polyphenols is
derived from in vitro or animal experiments, which are often
performed with doses much higher than those to which
humans are exposed through the diet [81–83]. Epidemi-
ologic studies tend to confirm the protective effects of poly-
phenol consumption against CVD [84]. Both antioxidant and
prooxidant effects of polyphenols have been described, with
contrasting effects on cell physiologic processes. As anti-
oxidants, polyphenols may improve cell survival; as pro-
oxidants, they may induce apoptosis and prevent tumor
growth [85]. However, the biological effects of polyphenols
may extend well beyond the modulation of oxidative stress.
There is a significant history regarding the well known
pomegranate fruit (Punica granatum L.) [86–91]. The
soluble polyphenol content of pomegranate juice (PJ) varies
within the limits of 0.2–1.0%, depending on variety, and
includes mainly anthocyanins, catechins, ellagic tannins, and
gallic and ellagic acids [87,88,91]. More importantly, PJ
possesses potent antioxidant activity that elicits antiathero-
ergic properties in mice [91–93] and can inhibit cycloox-
ygenases and lipoxygenases [89]. Prolonged supplementation
with PJ can largely correct the perturbed shear stress-induced
proatherogenic disequilibrium by increasing eNOS activity
and decreasing redox-sensitive transcription factors both in
vitro in cultured human coronary artery EC and in vivo in
 hypercholesterolemic mice [93,94].

Vascular disorders such as atherosclerosis cause disturbed
blood flow in the affected regions, and this leads to perturbed
shear stress that, in turn, causes endothelial damage [95]. Our
findings of reductions in macrophage foam cell formation,
oxidation-specific epitopes, and lesion area in atherosclerotic
prone lesion regions (low- and high-prone areas) in PJ-treated
mice [93] clearly confirm the correlation between antiox-
idative effects and antiatherogenic properties, elicited by PJ,
as was observed in other studies [91,92,96]. Modulation of
redox-sensitive transcription factors (ELK-1 and p-JUN) and eNOS expression is associated with antiatherogenic activity in such areas [93]. These effects are similar to those elicited by antioxidants (vitamins E and C) and L-arginine [20]. The antioxidant level in PJ was found to be higher than in other natural juices such as blueberry, cranberry, and orange, as well as in red wine [97]. Polyphenols from red wine can reduce LDL aggregation in vitro and in vivo [97–99], and PJ administered to hypertensive patients causes also a significant decline in systemic blood pressure [100]. PJ consumption for 3 years by patients with carotid artery stenosis reduced common carotid intima-media thickness, blood pressure, and LDL oxidation [101]. Accordingly, tea pigment (and possibly polyphenols) exerted some antiatherosclerotic effects [102]. More recently, it was shown that short- and long-term black tea consumption reverses endothelial dysfunction in CVD patients [103]. Similarly, the ingestion of polyphenols contained in purple grape juice had beneficial effects on endothelial function in patients with CHD [104]. Taken together, these data suggest that polyphenols can protect arteries from vascular damage via antioxidant effects and NO restoration.

However, certain large clinical trials using different antioxidants have failed to show any beneficial effects in terms of prevention of major CVD events [105,14,95]. One possible explanation of this divergence is that the models used in experimental studies, although very useful to study pathophysiological mechanisms, may not precisely reflect the disease in humans [105,14,95]. Alternatively, the doses of antioxidants used in those few studies may not have been appropriate, and/or the progression of disease may have been too severe. More recently, PJ has been shown to revert the potent downregulation of the expression of eNOS induced by LdLox in human coronary endothelial cells [106] suggesting that PJ can exert beneficial effects on the evolution of clinical vascular complications, CHD, and atherosclerosis in humans by enhancing the eNOS bioactivity. PJ, tested for its capacity to upregulate and/or activate eNOS in bovine pulmonary artery endothelial cells, elicited no effects on eNOS protein expression or catalytic activity thus indicating that PJ possesses potent antioxidant activity that results in marked protection of NO against oxidative destruction, thereby resulting in augmentation of the biological actions of NO [107]. Along with components of the PJ studied for their antioxidant properties, i.e., PJ sugar fraction and pomegranate polyphenolic phytochemicals, pomegranate by-product (PBP) which includes the whole pomegranate fruit left after juice preparation, determined a reduction in atherosclerotic lesion size by up to 57% and a reduced oxidative stress in the apolipoprotein E-deficient mice (E degrees) peritoneal macrophages [108–111]. Daily consumption of PJ by diabetic patients resulted in antioxidative effects on serum and macrophages [112] and improved stress-induced myocardial ischemia in patients who have CHD [113]. Thus, PJ and its by-products may improve redox status of the arterial cells (Fig. 1).

3.3. Dietary fiber

Recent cohort studies have found a consistent protective effect of dietary fiber on CVD outcomes, prompting many leading organizations to recommend increased fiber in the daily diet [114]. However, the biologic mechanisms explaining how a fiber influences the cardiovascular system have yet to be fully elucidated. Recent research in large national sample in the USA has demonstrated an association between dietary fiber and levels of C-reactive protein (CRP), a clinical indicator of inflammation. Epidemiologic evidence demonstrating that high-fiber diets are beneficial, coupled with this newer evidence of a possible metabolic effect on inflammatory markers, suggests that inflammation may be an important mediator in the association between dietary fiber and CVD. In the Nurses Health Study, women in the highest quintile of fiber intake (median 22.9 g/day) had an age-adjusted relative risk for major coronary events that was 47% lower than women in the lowest quintile (11.5 g/day) [115]. In a cross-sectional study to analyze the relation between the source or type of dietary fiber intake and CVD risk factors in a cohort of adult men and women, indicate that the highest total dietary fiber and insoluble dietary fiber intakes were associated with a significantly lower risk of overweight and elevated waist-to-hip ratio, blood pressure, plasma apolipoprotein (apo) B, apo B:apo A–I, cholesterol, triacylglycerols, and homocysteine [116]. Soluble fiber, i.e., beta-glucans, pectin, decreases serum total and low-density lipoprotein cholesterol concentrations and improves insulin resistance. Practical recommendations for CVD prevention include food-based approach favoring increased intake of whole-grain and dietary fiber (especially soluble fiber), fruit, and vegetables providing a mixture of different types of fibers [117,118].

3.4. Fatty acids

Evidence from epidemiologic and clinical secondary prevention trials suggests n-3 PUFAs may have a significant role in the prevention of CHD [reviewed in 119]. Dietary sources of n-3 PUFAs include fish oils, rich in eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), along with plants rich in α-linolenic acid. Randomized secondary prevention clinical trials with fish oils (eicosapentaenoic acid, docosahexaenoic acid) and α-linolenic acid have demonstrated reductions in risk that compare favorably to those seen in landmark secondary prevention trials with lipid-lowering drugs. The anti-inflammatory activity of fish oil may vary among different sources due to variations in EPA/DHA content [120]. PUFAs, and especially total n-3 fatty acids, were independently associated with lower levels of proinflammatory markers (IL-6, IL-1ra, TNF-α, C-reactive protein) and higher levels of anti-inflammatory markers (soluble IL-6, IL-10, TGFβ) [121]. Several mechanisms explaining the cardioprotective effect of the n-3 PUFA have been suggested including antiarrhythmic and antithrombotic
roles. n-3 PUFA s have been recently shown to directly inhibit vascular calcification via p38-MAPK and PPAR-gamma pathways, and to reduce gene expression of cyclooxygenase-2, an inflammatory gene involved in plaque angiogenesis and plaque rupture through the activation of some metalloproteinases and reduction of oxidative stress (Fig. 1). The quenching of gene expression of pro-inflammatory proatherogenic genes by omega-3 fatty acids has consequences on the extent of leukocyte adhesion to vascular endothelium, early atherogenesis and later stages of plaque development and plaque rupture, ultimately yielding a plausible comprehensive explanation for the vasculoprotective effects of these nutrients [122,123]. The modulation of channel activities, especially voltage-gated Na(+) and L-type Ca(2+) channels, by the n-3 PUFA may explain, at least partially, the antiarrhythmic action [124]. It does seem clear from recent prospective randomized trials that both fish and plant sources of n-3 PUFA s can favorably impact CV health [125–127]. Although official US guidelines for the dietary intake of n-3 PUFA is not available, several international guidelines have been published. Fish is an important source of the n-3 PUFA in the US diet; however, vegetable sources including grains and oils offer an alternative source for those who are unable to regularly consume fish. Table 1 shows a summary of randomized clinical trials examining the effects of dietary interventions with fatty acids on biomarkers of inflammation [128–145].

3.5. Ethanol and nonethanolic components of wine

During the last decade, several groups have reported that, in animal models of myocardial ischemia/reperfusion, certain nutrients, including ethanol and nonethanolic components of wine, may have a specific protective effect on the myocardium, independent of the classical risk factors implicated in vascular atherosclerosis and thrombosis [146]. Mechanisms through which the consumption of alcoholic beverages protects against ischemia-induced cardiac injury are not yet fully characterized. The protective effect of alcohol has been primarily explained by an action on blood lipids (increase in high-density lipoprotein levels) and platelets (decreased aggregation) resulting in a reduced rate of coronary artery obstruction [147–149]. Other mechanisms are probably involved. Moderate alcohol has been shown to improve postischemic myocardial systolic and diastolic function in rats and to attenuate the post-ischemic reduction in coronary vascular resistance [150]. Moderate drinking may improve the early outcomes after acute myocardial infarction and prevent sudden cardiac death [151], suggesting a direct effect of ethanol on the ischemic myocardium that has been referred to as ‘ethanol preconditioning’ [152]. To date, adenosine type 1 (A1) receptors, alpha(1)-adrenoceptors, the epsilon isoform of protein kinase C (PKC), and adenosine triphosphate-dependent potassium (KATP) channels have been shown to mediate cardioprotection associated with chronic ethanol ingestion [153,154]. Both alcohol and polyphenolic antioxidant components contribute to the cardioprotective effects of wine compared to other alcoholic beverages (Fig. 1). The polyphenolic antioxidants present in red wine provide cardioprotection by their ability to function as in vivo antioxidants while its alcoholic component or alcohol by itself imparts cardioprotection by adapting the hearts to oxidative stress. Moderate alcohol consumption induced significant amount of oxidative stress to the hearts which was then translated into the induction of the expression of several cardioprotective oxidative stress-inducible proteins including heat shock protein (HSP) [155]. Other studies suggested anti-inflammatory and/or antioxidant effects of moderate drinking [146]. One major open question is whether ethanol and nonethanolic components of wine are cardioprotective, at least in part, by interfering with the myocardial prooxidant/antioxidant balance.

Important concepts, such as cardiac preconditioning, are now entering the field of nutrition, and recent experimental evidence suggests that ethanol and/or nonethanolic components of wine might exert preconditioning effects in animal models of myocardial ischemia/reperfusion. There is no doubt that such an observation, if confirmed in human subjects, might open new perspectives in the prevention and treatment of ischemic CHD.

4. Physical exercise and CVD

Regular physical activity causes substantial performance-improving and health-enhancing effects. Most of them are highly predictable, dose-dependent and generalizable to a wide range of population subgroups. Many of the biological effects of regular, moderate physical activity translate into reduced risk of CHD, cerebrovascular disease, hypertension, maturity onset diabetes, overweight and obesity, and osteoporosis. In the genesis of these conditions, a lack of physical activity and inadequate nutrition act synergistically and in part additively, and they operate largely through the same pathways [156]. Indeed, numerous studies have demonstrated a reduced rate of initial CHD events in physically active people [7,8,157]. These findings, along with those from studies that demonstrate biologically plausible cardioprotective mechanisms, provide strong body of evidence that regular physical activity of at least moderate intensity reduces the risk of CVD major events, thus leading to the conclusion that physical inactivity is a major CHD risk factor. Fig. 2 shows changes in cellular NO, ROS, and scavenger levels in relation to physical exercise degree (strenuous, moderate, or none) indicating reduction of oxidative stress in moderate physical activity. An even greater impact is seen when the endurance exercise program is of sufficient intensity and volume to improve aerobic capacity.

Molecular events associated with physical exercise effects on both endothelium and muscle function, such as high phosphate metabolism and reduced vascular expression of NAD(P)H oxidase can be altered by stopping regular exercise [158,159]. Data from the Health Professionals’
Follow-up Study [160] also provide robust evidence that as little as 30 min per week of strength training may reduce the risk of an initial coronary event. Guidelines for prescribing aerobic and resistance exercise for patients with CVD are available elsewhere [156,161].

4.1. Exercise programming recommendations

Specific integrating exercise programming activity recommendations are available for women [162], older adults [163], patients with CHF and heart transplants [164], stroke survivors [165], and patients with claudication induced by peripheral arterial disease [166]. Exercise training and regular daily physical activities are essential for improving a cardiac patient’s physical fitness. The occurrence of major CVD events during supervised exercise in contemporary programs ranges from 1:50 000 to 1/120 000 patient-hours of exercise, with only 2 fatalities reported per 1.5 million patient-hours of exercise [167]. Contemporary risk-stratification procedures for the management of CHD

Table 1

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Type and duration of dietary intervention/enrichment</th>
<th>Change in biomarkers of Inflammation</th>
<th>[Ref.]</th>
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<tbody>
<tr>
<td>Saturated and trans fatty acids</td>
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<tr>
<td>Healthy adult males</td>
<td>Control diet (30% fat) or experimental diets (39% fat) with 8% substitution of oleic acid, trans fatty acids, saturated fatty acids, stearic acid, or trans + stearic acid; 5 weeks</td>
<td>↑ CRP and E-selectin levels with trans fat diet compared with control; ↑ fibrinogen in stearic acid diet vs control; no difference in any marker between oleic acid diet and control; (P&lt;0.05)</td>
<td>[128]</td>
</tr>
<tr>
<td>Moderately hypercholesterolemic adults</td>
<td>Experimental diets (30% fat) two-thirds fats substituted with soybean oil, semi-liquid margarine, soft margarine, shortening, stick margarine, or butter; 35 days</td>
<td>No effect on CRP with any dietary fat type (P&gt;0.05)</td>
<td>[129]</td>
</tr>
<tr>
<td>Moderately hypercholesterolemic adults</td>
<td>Experimental diets (30% fat) two-thirds fats substituted with soybean oil, soybean oil-based stick margarine, or butter; duration 32 days</td>
<td>↑ IL-6 and TNF-α with stick margarine diet vs soybean oil diet (P&lt;0.05)</td>
<td>[130]</td>
</tr>
<tr>
<td>Type 2 diabetic patients and matched healthy subjects</td>
<td>High-fat diet (59% fat) or high-carbohydrate diet (73% carbohydrates), with or without antioxidants; 4-day study, 1 week apart</td>
<td>↑ IL-6, TNF-α, ICAM-1, VCAM-1 in healthy and diabetic subjects with high-fat meal; increased levels only in diabetics with high-carbohydrate meal (P&lt;0.05)</td>
<td>[131]</td>
</tr>
</tbody>
</table>

Monounsaturated fatty acids | | No effects (P>0.05) | |
| Healthy adult males | Mediterranean diet group or written advice-only group; 1 year | | |
| Patients with metabolic syndrome | Mediterranean-style diet or prudent diet; 2 years | ↑ hs-CRP, IL-6, IL-7, IL-18, with Mediterranean diet vs prudent diet (P<0.05) | [133] |

Polyunsaturated fatty acids | | | |
| Moderately hypercholesterolemic adults | ALA-enriched (15% ALA, 46% LA) or LA-enriched (58% LA, 0.3% ALA) margarine; 2 years | ↑ CRP in the ALA group vs LA (P<0.05) | [134] |
| Hypercholesterolemic adults | ALA diet (6.5% ALA, 10.5% LA), LA diet (12.6% LA, 3.6% ALA) or AAD (7.7% LA, 0.8% ALA); 6 weeks | ↑ CRP, VCAM-1, and E-selectin in ALA group vs LA; decreased ICAM-1 in ALA and LA groups vs AAD (P<0.05) | [135] |
| Healthy subjects | 1.5 g EPA+DHA, with or without 800 IU all-rac alpha-tocopherol; 12 weeks | No effects (P>0.05) | [136] |
| Obese men | 1.35 g of EPA+DHA or placebo capsules; 6 weeks | No effects (P>0.05) | [137] |
| Men and postmenopausal women | 1.5 g EPA+DHA or placebo; 12 weeks | No effects (P>0.05) | [138] |
| Male dyslipidemic patients | 15 mL linseed oil (8 g ALA) or 15 mL safflower oil (11 g LA); 12 weeks | ↑ CRP, SAA, and IL-6 in ALA group; no effects with LA (P<0.05) | [139] |
| Treated-hypertensive type 2 diabetic subjects | 4 g, DHA, or placebo; 6 weeks | No effects (P>0.05) | [140] |
| Postmenopausal women using HRT | 1.33 g EPA+DHA, or 2.56 g EPA+DHA, or placebo; 5 weeks | ↑ CRP and IL-6 with fish oil vs placebo (P<0.05) | [141] |
| Obese and lean normolipidemic men | 4 g EPA+DHA, with or without atorvastatin (40 mg); 6 weeks | ↑ CRP and IL-6 with fish oil + atorvastatin, but not with fish oil alone (P<0.05) | [142] |
| Conjugated linoleic acid | | | |
| Healthy volunteers | 4.2 g CLA isomer mixture or placebo; 12 weeks | ↑ CRP with CLA mixture vs placebo (P<0.01); no effects on TNF-α and VCAM-1 (P>0.05) | [143] |
| Adults with diet-controlled type 2 diabetes | 3.0 g CLA isomer mixture or placebo; 8 weeks | ↑ CRP with CLA mixture vs placebo (P<0.01); no effects on TNF-α and VCAM-1 (P>0.05) | [144] |
| Men with metabolic syndrome | 3.4 g CLA, or 3.4 g purified r10c12 CLA, or placebo; 12 weeks | ↑ CRP with r10c12 CLA supplementation vs placebo (P<0.01) | [145] |

AAD indicates average American diet; HRT, hormone replacement therapy. ↑ (increased) and ↓ (decreased).
help to identify patients who are at increased risk for exercise-related cardiovascular events and who may require more intensive cardiac monitoring in addition to the medical supervision provided for all cardiac rehabilitation program participants [168]. Supervised rehabilitative exercise for 3 to 6 months generally is reported to increase a patient’s peak oxygen uptake by 11% to 36%, with the greatest improvement in the most deconditioned individuals [169]. Improved fitness enhances a patient’s quality of life and even can help older adults to live independently [170]. Improved physical fitness also is associated with reductions in submaximal heart rate, systolic blood pressure, and rate-pressure product (RPP), thereby decreasing myocardial oxygen requirements during moderate-to-vigorous activities of daily living [171]. Furthermore, improvement in cardiorespiratory endurance on exercise testing is associated with a significant reduction in subsequent CVD fatal and nonfatal events independent of other risk factors [172–175]. These findings also apply to patients with CHF. In a recent meta-analysis of 81 studies involving 2587 patients with stable CHF [176], it was demonstrated a trend toward increased survival associated with improved functional capacity, as well as a reduction in cardiorespiratory symptoms after aerobic and strength training. Physical activity can be recommended as a preventive therapy to people of all ages. However, one serious concern related to the fact that physical exercise program should be administered cautiously and gradually in patients with long-term established sedentary style of life.

4.2. Aerobic fitness

There is incontrovertible evidence from observational and randomized trials that regular physical activity contributes to the primary and secondary prevention of CVD and is associated with a reduced risk of premature death. Physical fitness refers to a physiologic state of well-being that allows one to meet the demands of daily living (health-related physical fitness) or that provides the basis for sport performance (performance-related physical fitness), or both. Aerobic fitness refers to the body’s ability to transport and use oxygen during prolonged strenuous exercise or work whereas anaerobic fitness refers to the body’s ability to produce energy without the use of oxygen. Recent researchers have proposed that anaerobic capacity plays an important role in the performance of many activities of daily living [177,178]. Maximum anaerobic power (the maximum rate at which energy is produced without the use of oxygen) is generally taken as the standard measure of anaerobic fitness. Aerobic fitness is commonly measured by a person’s maximum aerobic power (VO2max), the maximum amount of oxygen that can be transported and used by the working muscles. The direct assessment of VO2max is generally conducted with the use of commercially available metabolic carts and requires highly trained staff. Owing to the complexity and cost of the direct assessment, many health and fitness professionals prefer to estimate VO2max without measuring oxygen consumption. A variety of tests are available to measure aerobic fitness indirectly, including submaximal tests (e.g., the Rockport One Mile Test, the modified Canadian Aerobic Fitness Test and the YMCA cycle ergometer protocol) and incremental to maximal tests (i.e., the Bruce protocol) that involve a variety of exercise modalities (i.e., cycling, running, stair climbing, rowing). Often heart rate is used to estimate VO2max during submaximal or maximal exercise tests. A lower heart rate for a given workload is thought to represent a higher level of aerobic fitness. Many fitness and health professionals prefer to use exercise time or estimated oxygen cost (i.e., metabolic

![Fig. 2. Different effects of physical exercise on redox status of the cell. Abbreviations: ROS, reactive oxygen species. NO, nitric oxide.](https://academic.oup.com/cardiovascres/article-abstract/73/2/326/486833)
equivalents [METs]) for the last stage completed during an incremental protocol to estimate aerobic fitness. To achieve a reasonable and reliable estimate of VO$_{2\text{max}}$, these indirect assessments must be conducted in a highly standardized and reproducible fashion.

Musculoskeletal fitness can be assessed relatively easily within and outside of the laboratory setting. Common tests include grip strength, push-ups, curl-ups (muscular endurance) and sit-and-reach tests (flexibility). Health practitioners should be aware that there are subtle differences between patient groups with respect to fitness testing. A series of field tests have been developed (i.e., the Leger 20-m shuttle test [179]) that provide valid and reliable determinants of aerobic fitness. In addition, it may be best to ask children to perform running activities instead of cycling activities because of their less developed muscular strength [180]. The American College of Sports Medicine has outlined special considerations that must be taken when assessing the physical fitness of elderly people [181]. Aging people are at increased risk of arrhythmias during exercise, and they commonly use medications that may affect physiologic responses to exercise. It is preferable to use equipment that promotes safety (e.g., treadmills with handrails, cycle ergometers). For obese people, one must be aware of the effect of obesity on their ability to conduct certain tests and the physiologic response to exercise. Obese people may also be prone to orthopedic injuries, and their heart rate response to exercise may differ from that of nonobese people [182].

4.3. Physical exercise lifestyle

Special care must also be taken during the assessment of people with chronic disease. For instance, patients with CVD should be monitored closely during physiologic testing. The appraiser must have a clear understanding of the effects of the patient’s clinical status and medications on the physiologic response to exercise. Low-intensity exercise is generally better accepted by people naive to exercise training, those who are extremely deconditioned (“out of shape”) and older people. Low-intensity exercise may result in an improvement in health status with little or no change in physical fitness. Indeed, light or moderate activity is associated with a reduced risk of death from any cause among men with established CHD. Furthermore, regular walking or moderate to heavy gardening has been shown to be sufficient in achieving these health benefits [183]. Low-fit people can

Table 2
Relative intensity of effort and representative 7-month exercise program

Panel A. Relative intensities for aerobic exercise prescription (for activities lasting up to 60 min)

<table>
<thead>
<tr>
<th>Intensity (*range required for health)</th>
<th>% HR max</th>
<th>Category-ratio RPE scale</th>
<th>Breathing rate</th>
<th>Body temperature</th>
<th>Example of activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very light effort</td>
<td>&lt;35</td>
<td>&lt;2</td>
<td>Normal</td>
<td>Normal</td>
<td>Dusting</td>
</tr>
<tr>
<td>Light effort*</td>
<td>35–54</td>
<td>2–3</td>
<td>Slight increase</td>
<td>Start to feel warm</td>
<td>Light gardening</td>
</tr>
<tr>
<td>Moderate effort*</td>
<td>55–69</td>
<td>4–6</td>
<td>Greater increase</td>
<td>Warm</td>
<td>Brisk walking</td>
</tr>
<tr>
<td>Vigorous effort*</td>
<td>70–89</td>
<td>7–8</td>
<td>More out of breath</td>
<td>Quite warm</td>
<td>Jogging</td>
</tr>
<tr>
<td>Very hard effort</td>
<td>&gt;89</td>
<td>9</td>
<td>Greater increase</td>
<td>Hot</td>
<td>Running fast</td>
</tr>
<tr>
<td>Maximal effort</td>
<td>100</td>
<td>10</td>
<td>Completely out of breath</td>
<td>Very hot, perspiring heavily</td>
<td>Sprinting all-out</td>
</tr>
</tbody>
</table>

Panel B. Example of a 7-month exercise program for a healthy adult

<table>
<thead>
<tr>
<th>Program stage</th>
<th>Length of program (wk)</th>
<th>Frequency (day s/wk)</th>
<th>% HR$_{\text{max}}$</th>
<th>RPE</th>
<th>Breathing rate</th>
<th>Time per session/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial stage</td>
<td>1</td>
<td>3</td>
<td>60</td>
<td>2–4</td>
<td>Slightly increased</td>
<td>20</td>
</tr>
<tr>
<td>Perform light muscular endurance activities</td>
<td>2</td>
<td>3</td>
<td>60</td>
<td>3–5</td>
<td>Noticeable increased</td>
<td>20</td>
</tr>
<tr>
<td>Engage in aerobic exercise of light to moderate intensity</td>
<td>3</td>
<td>3</td>
<td>65</td>
<td>3–5</td>
<td>Noticeable increased</td>
<td>25</td>
</tr>
<tr>
<td>Improvement</td>
<td>5–7</td>
<td>4</td>
<td>70</td>
<td>3–5</td>
<td>Noticeable increased</td>
<td>25</td>
</tr>
<tr>
<td>Increase exercise intensity and duration with improved fitness</td>
<td>8–10</td>
<td>4</td>
<td>70</td>
<td>3–5</td>
<td>Noticeable increased</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>11–13</td>
<td>3–5</td>
<td>75</td>
<td>4–6</td>
<td>Noticeable increased</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>14–16</td>
<td>3–5</td>
<td>75</td>
<td>4–6</td>
<td>Noticeable increased</td>
<td>30</td>
</tr>
<tr>
<td>Try to achieve health and fitness goals</td>
<td>17–20</td>
<td>3–5</td>
<td>75</td>
<td>4–8</td>
<td>More difficult talking while exercising</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>21–24</td>
<td>3–5</td>
<td>80</td>
<td>4–8</td>
<td>More difficult talking while exercising</td>
<td>35</td>
</tr>
</tbody>
</table>

Maintenance

Try to maintain health-related fitness

24–28 | 3–5 | 80 | 4–8 | More difficult talking while exercising | 40 |

Created with modification from information provided in the handbook for Canada’s Physical Activity Guide to Healthy Active Living, and the American College of Sports Medicine’s guidelines for exercise testing and prescriptions [157,160–163].

Abbreviations: HR max=maximum hearth rate, RPE=patient’s rating of perceived exertion, wk=week.
attain significant improvements in physical fitness with a lower training intensity (e.g., 40%–50% of heart rate reserve) than that needed by people with a higher baseline fitness level, whereas the latter would need a greater level of exercise intensity to achieve further improvements in fitness [184,185]. Deconditioned people may improve physical fitness with as little as 2 exercise sessions per week [186]. In fact, some have shown an improvement in aerobic fitness with exercise intensities as low as 30% of heart rate reserve in sedentary people [187]. However, adherence to this form of exercise may be poor and the risk of musculoskeletal injury high, especially in people unaccustomed to exercise [188,189]. Many health professionals recommend a minimum level of energy expenditure of about 1000 kcal (4200 kJ) per week, acknowledging the additive benefits of higher levels of energy expenditure. Expending 1000 kcal (4200 kJ) per week is equivalent to 1 h of moderate walking 5 days a week. However, a lower level may also achieve health benefits [190]. The American College of Sports Medicine has stated that health benefits occur with energy expenditures as low as 700 kcal (2940 kJ) per week, with additional benefits occurring at higher levels [184]. The recommended daily energy expenditure for health is currently 150–400 kcal (630–1680 kJ) per day [180]. For instance, if a previously sedentary person exercised at the lower end of the recommended amount (150 kcal [630 kJ]) on most days of the week, he or she would approach the health-related goal of 1000 kcal (4200 kJ) per week, with additional benefits occurring at higher levels [184]. The ability to predict outcomes in patients with CVD remains imperfect. Some research questions yet remaining include the identification of optimal genetic determinants or biomarkers for predicting CVD and a better understanding of how gene–environment interaction can influence CVD. The well-being of general population necessarily comes from adequate physical activity together with careful nutritional habits.

Subjective indicators of the relative intensity of effort are shown in Table 2 (Panel A). For instance, participants are often prescribed exercise that they perceive to be of moderate intensity. The most commonly used scale is the RPE (rating of perceived exertion) scale [192,193]. An example of a 7-month exercise prescription that incorporates objective and subjective indicators of exercise intensity is provided in Table 2 (Panel B) for a healthy adult starting an exercise program. The general principles for healthy adults can be applied in the training of patients with CVD. Such patients should engage in 20–60 min of exercise on most days of the week. An energy expenditure of about 1600 kcal (6720 kJ) per week has been shown to effectively halt the progression of coronary artery disease, and an expenditure of 2200 kcal (9240 kJ) per week has been associated with plaque reduction and a reversal of the disease [194,195]. There are, however, slight differences in the exercise prescription model for patients with CVD. The duration of each session depends on the clinical status of the patient [196]. The minimal training intensity threshold is about 45% of the heart rate reserve for patients with CHD [195], compared with 30% of the heart rate reserve for unfit healthy people [187]. This difference is thought to be the result of the difficulty for CVD patients in achieving true maximum effort during a stress test [187]. A similar intensity is used for CHF patients when they begin many traditional rehabilitation programs. Additional benefits, however, are likely achieved with higher exercise intensities, if tolerated and safe for the patient [195].

5. Conclusions

Unfortunately, in Western countries the high CVD prevalence is largely attributable to the contemporary lifestyle which is often sedentary, and includes a diet high in saturated fat and sugar, and low in n-3 PUFAs, fruit, vegetables and fiber. In combination with drug treatment, intervention in the area of nutrition and physical activity is the recommended treatment for patients at a high risk of CVD. Any strategy that can influence health maintenance is of interest, especially lifestyle factors such as nutrition, exercise or stress control. Integrated actions against risk factors (i.e., smoking, physical inactivity, and unhealthy diet), implemented within the social context, can lead to the reduction of major CVD events. Growing evidence clearly indicates that antioxidants, dietary fibers, polyphenols contained in the PJ, n-3 PUFAs, wine, vitamins, and minerals, together with physical exercise reduce risk factors for CVD.

However, some large-scale clinical trials in subjects with advanced atheroma failed to confirm the protective effects of some antioxidants. Because of the extremely long history of CVD, the causal relationship of nutrition/physical exercise on major CVD events is still difficult to assess prospectively. The ability to predict outcomes in patients with CVD remains imperfect. Some research questions yet remaining include the identification of optimal genetic determinants or biomarkers for predicting CVD and a better understanding of how gene–environment interaction can influence CVD. The well-being of general population necessarily comes from adequate physical activity together with careful nutritional habits.

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