Prevention of cardiovascular diseases: Role of exercise, dietary interventions, obesity and smoking cessation

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Hypertension, myocardial infarction, atherosclerosis, arrhythmias and valvular heart disease, coagulopathies and stroke, collectively known as cardiovascular diseases (CVDs), contribute greatly to the mortality, morbidity and economic burden of illness in Canada and in other countries. It has been estimated that over four million Canadians have high blood pressure, a comorbid condition that doubles or triples the risk of CVD. According to the Heart and Stroke Foundation of Canada, CVDs caused 36% of deaths in 2001 and were responsible for 18% of the total hospital costs in Canada. The majority of Canadians exhibit at least one CVD-related risk factor, such as tobacco smoking, physical inactivity, diabetes, obesity, hypertension, a lack of daily fruit and vegetable consumption, and psychosocial factors, making these people more prone to developing a serious CVD-related illness in the future. It is therefore important that CVD-related causes and concerns be addressed. Given the scope and prevalence of CVDs, it is obvious that a population health approach – 'prevention is better than cure' – would be the most appropriate model to adopt to deal with this ubiquitous health problem and to reduce the costs of hospitalization, long-term medication and rehabilitation. The focus of the present review is to evaluate and compare the results of epidemiological, experimental and clinical studies, reporting on the influence of physical activity, dietary intervention, obesity and cigarette smoking on cardiovascular health and the prevention of CVDs. The prophylactic measures must be dealt with collectively because there is overwhelming evidence that the occurrence of CVDs can be reduced by approximately 80% by making lifestyle modifications. The preventive strategies against CVDs must be targeted at a primary health promotion level before some of the important underlying causes of CVD seriously afflict a person or a population at large. Such preventive approaches would help in reducing not only employee absenteeism but also the hospital and drug costs burdening the health care systems of both developed and developing countries.

Key Words: *Cardiovascular disease; Diabetes; Diet; Exercise; Obesity; Smoking cessation*

At the advent of the 21st century, infectious diseases became relatively less of a concern, while chronic diseases continue to plague the global populace. Antibiotics and many other drugs help to treat acute diseases, whereas the biomedical model is limited when dealing with the health crisis resulting from chronic diseases, which develop over a prolonged period of time and persist for lengthy durations. As opposed to their acute disease counterparts, most chronic diseases are largely related to lifestyle factors, and can be minimized or prevented, for the most part, by lifestyle changes.

Chronic diseases have one or more of the following characteristics: they are persistent and leave residual disability; they are caused by nonreversible pathological conditions; and they require special training of the patient on rehabilitation, or may be expected to require prolonged medical supervision, observation or health care (1). Among the most common chronic diseases that afflict humans worldwide are diabetes, cardiovascular diseases (CVDs), osteoporosis, arthritis, obesity, chronic obstructive pulmonary disease, inflammatory bowel disease, central nervous system degenerative diseases and some cancers. CVDs and chronic obstructive pulmonary disease not only contribute largely to morbidity and mortality but also put a heavy economic burden on the health care system at both a global and a national scale. As shown in Figure 1, CVDs caused 78,942 deaths (36% of all deaths) in Canada in 1999, and in 2000, CVDs were responsible for 18% of the total hospital costs in Canada (2-4). Therefore, it is important that CVD-related causes and concerns be addressed.

Given the scope and prevalence of CVDs, it is clear that a population health approach, using preventive measures, would be the most appropriate model to adopt to deal with this ubiquitous problem. The focus of the present review is to evaluate the influence of physical activity (exercise), dietary intervention, obesity and diabetes, and cigarette smoking on cardiovascular health and the prevention of CVDs. Prophylactic measures must be dealt with collectively because there is overwhelming evidence that the occurrence of CVDs can be reduced by making lifestyle changes. Thus, CVDs must be targeted at a primary health promotion level before some of the important underlying causes of CVD seriously afflict a person or a population at large. Such preventative approaches would help in reducing not only employee absenteeism but also the hospital and drug costs burdening the health care systems of Canada and many other countries.

With increasing longevity and growing elderly populations, patients with CVDs may require expensive treatment, such as cardiac bypass surgery, postoperative rehabilitation and lifelong medications. Health care professionals will continue to use their best judgement, knowledge of current scientific advances and the resources at hand to treat their patients who,

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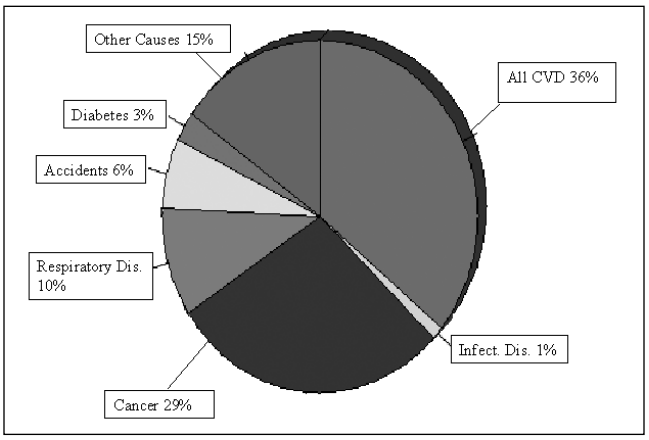

Figure 1) *Leading causes of death in Canada in 1999. Percentages represent data combined from males and females of all ages. CVD Cardiovascular disease; Dis Diseases; Infect Infectious. Data from reference 6*

when deemed neccessary, require medicines and surgeries. Nevertheless, alternative interventions reported in the scientific literature for the prevention of CVDs should also be explored with the aim to minimize physician supervision and associated diagnostic and hospitalization costs.

SCOPE AND PREVALENCE

CVDs contribute greatly to the mortality, morbidity and economic burden of illness globally. According to the World Health Organization (WHO), approximately 17 million people die annually as a result of CVDs (4,5). More than four million Canadians have high blood pressure (BP), a comorbid condition that doubles or triples the risk of CVD. In 2001, CVD caused 74,824 deaths in Canada, 33% of all deaths in males and 35% in females. To date, CVD remains the leading cause of death. Not only has CVD already wreaked havoc, but 80% of the Canadian population has at least one CVD-related risk factor (eg, tobacco smoking, physical inactivity or being overweight/obese), making these people more prone to developing serious CVD in the future (2). In 1998, the economic burden of treating CVD-related illness was over $18 billion in Canada (6). The economic burden of illness is measured by considering all direct and indirect costs related to this disease. Obviously, the costs of hospitalization and rehabilitation care for patients with CVD are very high in Canada, where universal health care is available to all Canadians. Because CVD often causes morbidity, persons affected by CVD are commonly forced to accept an inferior quality of life. Consequences of this lower standard of living are seen in measures of 'potential years of life lost', an index of the number of years lost by a person compared with normal life expectancy. For instance, CVD-related potential years of life lost was 294,000 in Canada in 1995. This figure has remained relatively stable and continues to put a severe strain on the nation's social and economic well-being (7).

RISK FACTORS ASSOCIATED WITH CVD

Multiple risk factors are attributed to causing CVD. According to the Canadian Heart and Stroke Foundation, the following are some of the most significant risk factors: age, sex, family history, tobacco smoking, physical activity, being overweight, diet, BP and diabetes (3). These risk factors fall into the categories of either nonmodifiable or modifiable risk factors. As described below, nonmodifiable risk factors consist of those conditions that a person cannot alter, whereas modifiable risk factors are conditions that can be altered by making certain lifestyle changes.

Nonmodifiable risk factors

Nonmodifiable risk factors include age, heredity or genetic makeup, and type 1 diabetes. Age is a predisposing factor for most chronic diseases because of the wear and tear the body undergoes over time (ie, making it more vulnerable to chronic ailments). With advancing age, the body is exposed to various strains and stressors, as well as free radicals generated in the body, which hasten the breakdown of cell and organ functions. Epidemiological research has shown that people who have a family history of heart disease and coagulopathies are more prone to developing CVDs. Additionally, if a person is afflicted by type 1 (juvenile) diabetes, several aspects of his or her body functions are compromised, primarily fat metabolism and glucose tolerance. Such metabolic disorders make the person more susceptible to developing CVDs.

Diabetes is on the rise worldwide. Across Canada, diabetes prevalence peaks with age, and 15.5% of Canadians between the ages of 75 and 79 years had the condition in 1999/2000. Diabetes was diagnosed in more than 5% of women and approximately 6% of men older than 20 years in Ontario in 2000 (8). Childhood obesity is also on the upswing in Canada and the United States. Type 2 diabetes and obesity are conditions largely dependent on lifestyle factors; therefore, society needs to take responsibility for advocating a healthy lifestyle, so as to minimize the occurrence of lifestyle-related chronic diseases.

Modifiable risk factors

The issue of potentially modifiable risk factors for CVD-related mortality and morbidity among different nationalities, their lifestyles and dietary habits has been the subject of innumerable epidemiological and clinical investigations. In 2003, the Canadian Heart and Stroke Foundation identified nine major modifiable risk factors for CVD, namely, tobacco smoking, alcohol abuse, physical inactivity, malnutrition, obesity, high BP, high concentrations of dietary fat and blood lipids, and high blood glucose concentrations (2). Sudden stress, frequent migraine and the use of oral contraceptives have also been identified as risk factors for the increased incidence of coronary disease and stroke (9,10).

A case-crossover study performed by Koton et al (9) showed that negative emotions, anger, sudden changes in body posture or startling events, all types of sudden stress, significantly increase the risk of the acute onset of ischemic stroke. A systematic review and meta-analysis of 14 studies (11 case-control and three cohort studies) showed that persons who regularly have migraines are at an increased risk of developing stroke, and a subgroup of women who have migraines and use oral contraceptives are at a greater risk of experiencing ischemic stroke (10).

In a landmark case-control study, Yusuf et al (11) determined the association between potential risk factors and acute myocardial infarction (MI) in 29,972 subjects (15,152 patients and 14,820 controls) from 52 countries in Asia, Europe, the Middle East, Africa, Australia, North America and South America. The results of this INTERHEART case-controlled

study showed that the two most important risk factors for MI are cigarette smoking and an abnormal ratio of blood lipids (apolipoprotein B to apolipoprotein A1), which together predict two-thirds (66%) of the global risk of heart attack. The additional seven risk factors for MI are diabetes, hypertension, abdominal obesity (waist to hip ratio), psychosocial factors (depression and stress), a lack of daily fruit and vegetable consumption, a lack of physical exercise and the amount of alcohol consumed. The authors concluded that these nine factors collectively predict 90% of the risk of a heart attack in men and 94% in women worldwide. They emphasized that the vast majority of heart attacks may be predicted by the nine measurable factors regardless of the geographical region, ethnic group, sex and age. As a corollary to this conclusion, Yusuf et al (11) stated that similar health promotion strategies can be applied globally for the prevention of premature death and disability associated with MI.

The INTERHEART study provides convincing evidence that CVD is preventable by lifestyle changes. Based on the findings of this large international case-controlled study, it appears that almost 90% (not 50% as was previously believed) of heart disease is caused by nine potentially modifiable risk factors. Through regular physical activity, eating a healthier diet and by not smoking, it is possible to profoundly reduce the risk of MI in both sexes and all age groups. Contrary to what was previously believed, heredity or the genetic makeup of a person does not play a major role in causing CVD. Therefore, it appears that if one's parents or siblings have or had heart disease, the other closely related persons are not necessarily bound to suffer the same fate.

In Canada and America, obesity, tobacco use and sedentary lifestyle are the leading preventable causes of morbidity and mortality. Other preventable causes of premature death and morbidity are type 2 diabetes and heart disease. Many of the modifiable risk factors are codependent, and altering one risk factor may change the degree of other risk factors. Therefore, cooperative efforts from the health care authorities, medical associations and family physicians, as well as the school boards and dieticians, are needed to mobilize and promote prophylactic measures surrounding modifiable risk factors. Such health promotion policies regarding children and adults, including exercise, healthy eating habits and eduction on nutrition, and smoking cessation, would not only help in minimizing hypertension, obesity and type 2 diabetes in the general population, but would also help in reducing the tremendous health care costs associated with the treatment of CVDs in developed and developing countries.

PHYSICAL ACTIVITY AND CVD

Physical activity or exercise is a part of everyone's life. However, it is the degree of physical exertion that differs among people. Several evidence-based studies have consistently indicated a positive correlation between physical activity and good health. Nevertheless, various aspects of physical activity must be considered when evaluating how well controlled studies have been conducted. Definitions of physical activity often vastly differ, rendering the results of different studies incomparable. Fortunately, there are three areas of interest that remain relatively consistent in defining physical activity, namely, intensity, duration and frequency. Intensity refers to the degree or extent of exertion and is often presented as a percentage of target heart rate or lung volume (ie, oxygen consumption [VO_2]). Duration refers to how long a particular activity is undertaken, and frequency refers to the number of times a given activity is performed. A multitude of studies (2-34) have been conducted showing a relationship between physical activity and overall well-being. It has been repeatedly shown that an inverse relationship exists between physical activity and the occurrence of CVDs (ie, with increased physical activity, the relative risk of developing CVD is decreased). With regard to specific surrogate markers and biological factors pertaining to CVD risk factors (eg, high BP, and increased cholesterol and triglyceride concentrations), clinical and laboratory evaluations have been performed to show the benefits of physical activity. Such quantitative measurements were performed to determine the influence of exercise on blood coagulation and fibrinolysis, vascular remodelling, BP and blood lipid profiles. Correspondingly, these studies have also shed light on the possible adverse consequences of exercise, especially when dealing with patients with chronic heart failure, and the precautions that should be taken to bypass these health risks (12-30).

Influence of exercise on blood coagulation and fibrinolysis

Blood coagulation and fibrinolysis are two important physiological functions influencing the formation and breakdown of clots within blood vessels. Fibrinolysis is an enzyme-activated phenomenon (12). Moreover, these hematological functions are influenced by various blood factors, which either inhibit or promote clot formation or breakdown. To understand the effectiveness of the mechansims of coagulation and fibrinolysis, serum concentrations of biomarkers such as plasma fibrinogen, factor VIII, factor VII, tissue plasminogen activator (t-PA), plasminogen activator inhibitor-1 (PAI-1) and fibrin D-dimer are measured (14). Blood platelet count and aggregation are also important aspects of optimal coagulation and fibrinolysis in the body (15). Inhibition of platelet aggregation plays a very important role in the prevention of heart attacks and strokes. Increased concentrations of fibrinogen, platelet aggregation or activation, factor VII, factor VIII and PAI-1 increase the probability of intravascular coagulation. On the other hand, increased serum concentrations of t-PA increase the probability of fibrinolysis; specifically, t-PA is responsible for promoting the activity of plasminogen, an enzyme that actively dissolves unwanted blood clots. PAI-1 inhibits the action of t-PA by binding to it and rendering it inactive. The remaining coagulation factors effectively act to build a clot by causing the aggregation of platelets and by forming the rigid network that is the basis of blood clot formation (12). A balance in the serum concentrations of coagulation and fibrinolytic factors is important because they seem to be directly correlated to the risk of cardiovascular ischemic events such as stroke and MI. Clotting and fibrinolytic factors play a pivotal role in the formation of thrombi and emboli (13). Hence, in patients with CVD, it is essential to ensure that a proper balance of these blood constituents is maintained. Several studies have attempted to show the influence of exercise on blood coagulation and fibrinolysis and, overall, positive effects of physical activity have been reported (12-16).

El-Sayed et al (13) have studied the specific effects of exercise on plasma fibrinogen concentrations. They found a significant reduction in plasma fibrinogen concentration from 266.3±14.5 mg/dL to 222.2±23.9 mg/dL ($P<0.05$) under optimal exercise conditions (at maximum VO_2 [VO_2max] for 30 min). Under suboptimal exercise conditions (at 75% of

VO_2max for 30 min), the fibrinogen concentration decreased from 239.5±45.4 mg/dL to 209.7±42.4 mg/dL (P<0.05). These results show a positive effect of exercise on plasma fibrinogen concentrations. The lower the concentration of fibrinogen content, the lesser the risk of thrombus formation, which consequently reduces the possible risk of ischemic cardiac events.

Wang et al (15) attempted to show a relationship between platelet function and exercise training in 23 healthy men aged 21 to 23 years. Platelet adhesiveness and aggregability were the main determinants of the study. The results indicated that short-term acute exercise in a group of subjects (n=12) who participated solely in exercise tests every four weeks, without a regular form of physical activity, experienced increased platelet adhesiveness and aggregability. This acute exercise scenario appears to create a sudden stress on the body, inducing a 'fight or flight response', whereby clotting factors would be increased to protect against possible injury. However, as people became accustomed to a long-term exercise regimen (60% of VO_2max for 30 min/day, five days per week for eight weeks), both platelet characteristics being investigated were decreased. This study was further extended to examine the detraining of platelet function. Detraining lasted for a period of 12 weeks, wherein the exercise regimen was stopped. It was found that detraining caused the platelet adhesiveness or aggregability to rebound back to normal levels after 12 weeks. These findings suggest that moderate physical activity can be beneficial in reducing risk factors associated with thromboembolic disorders. Furthermore, the detraining information supports the use of exercise over a prolonged period of time, indicating that moderate daily exercise (30 min/day) should be made a part of a person's lifestyle.

A review by Womack et al (12) examined multiple factors linked with coagulation and fibrinolysis. Overall, the review showed that, compared with sedentary people, those who took part in regular physical activity tended to exhibit more effective fibrinolytic profiles and a decreased potential for resting clot formation. In sedentary people, the fibrinolytic capacity was reduced while the plasma concentrations of PAI-1 were increased, possibly leading to a larger coagulation potential. However, Wang et al (15) also found that exercise over short sudden bouts (acute exercise) was followed by increased coagulation potential.

DeSouza et al (14) reported the influence of physical activity on coagulation and fibrinolytic factors in 51 healthy women aged 27 to 63 years. The authors also attempted to show age-related differences in physical activity. Markedly different fibrinogen plasma concentrations were found between postmenopausal sedentary women and postmenopausal physically active women. Postmenopausal physically active women had significantly lower plasma fibrinogen concentrations than postmenopausal sedentary women (2.49±0.09 g/L versus 2.85±0.09 g/L, P<0.01). It therefore appears that postmenopausal sedentary women may be at a greater risk of developing thrombi. With regard to fibrinolytic systems, the postmenopausal sedentary women had markedly higher PAI-1 concentrations (14.5±1.2 AU/mL versus 6.5±1.1 AU/mL, P<0.01) and significantly lower t-PA concentrations (1.3±0.1 U/mL versus 2.7±0.4 U/mL, P<0.01) than the postmenopausal physically active women. Each of these plasma factor profiles increased the potential coagulation risk and reduced the fibrinolytic capacity of the postmenopausal sedentary women.

When considered together, the findings of the above mentioned studies show that the probability of ischemic events or stroke is decreased with long-term regular exercise. The results of these studies also substantiate the need for regular physical activity and provide scientific evidence to support a possible reduction in thrombus formation with exercise. The reduction in thrombus formation is attributable to exercise-induced increases in t-PA and decreases in PAI-1, lower plasma fibrinogen concentrations, and decreases in the adhesion or aggregation properties of platelets.

Influence of exercise on vascular remodelling

Vascular remodelling is an old concept in the area of cardiovascular research. Components of vascular remodelling include angiogenesis, vasculogenesis and arteriogenesis. Angiogenesis pertains to the growth of new capillaries from pre-existing capillaries. Angiogenesis is considered an important aspect in the oncology discipline and is used as a therapeutic strategy to minimize the growth of new blood vessels around a neoplasm, thus causing shrinkage of the tumour due to curtailed blood supply. However, with regard to cardiovascular health, the aim of cardiovascular remodelling is to maximize angiogenesis to increase the level of perfusion in the cardiovascular tissues and cells, thereby reducing the detrimental effects of ischemia. Vasculogenesis not only involves the formation of new blood vessels in their original position but also involves the growth of endothelial progenitor cells (EPCs) (19). Arteriogenesis involves the modification of pre-existing arterioles, and this process affects the size, length and diameter of arterioles; however, the modified arterioles are invariably occluded before these adaptations (21). Recently, several studies have been conducted to determine the effects of exercise on vascular remodelling. Although these studies were mainly performed in animals, evidence also points to parallel findings in humans.

It is now well recognized that cellular mediators control vascular remodelling, like many other physiological functions of the body. The most commonly known mediators for vascular remodelling are cytokines, vascular endothelial growth factor (VEGF) and fibroblast growth factor. VEGFs are a family of glycoproteins that activate EPCs, causing them to fuse to pre-existing capillaries and eventually generate new vascular cells and blood vessels. The fibroblast growth factors act as cell surface ligands that, like VEGFs, act on endothelial cells to stimulate the production of various enzymes essential for the digestive processes associated with angiogenesis (19).

Miyachi et al (18) showed that endurance training over time results in vascular remodelling in humans. Specifically, arteriogenesis occurred causing the cross-sectional area (CSA) of various arteries to increase. The results of this study revealed a 16% increase in the CSA of the ascending aorta and a 24% increase in the CSA of the abdominal aorta. The study was carried out in 12 healthy men aged 20 to 24 years. These CSA increases were seen only in the exercise-trained subjects (n=7), whereas the sedentary subjects (n=5) did not exhibit any evidence of vascular remodelling. The authors hypothesized that increases in blood velocity through the arteries may heighten the risk of CVD. However, the findings showed that the amount of blood flow through the arteries dramatically increased by up to 20% in exercising men. Arterial dilation counteracted the potential increase in velocity, because resistance to the increased blood flow was reduced. Repeated measurements by using Doppler ultrasonograms

were made to assess the velocity of the blood travelling through the ascending aorta. The results of this investigation showed that by inducing arteriogenesis through exercise, it is possible to increase blood flow to those areas of the body that may previously have been experiencing ischemia. Additional studies in different age groups are needed to substantiate these findings on arteriogenesis.

Dinenno et al (20) conducted a study in 108 men to assess the effect of exercise on vascular remodelling. The participants were divided into an endurance-trained or sedentary group. To determine whether physical activity had any influence on vascular remodelling, the investigators measured the diameter and intima-media thickness of the femoral artery from images generated from an ultrasound machine. They found that the prolonged endurance training of 55 athletes, who were distance runners and/or triathletes training heavily and competing in local races, caused the lumen diameter of the blood vessel to increase, whereas the arterial wall thickness decreased. Measurements showed that in the endurance-trained people, the lumen diameter of the femoral artery was 9.62±0.12 mm compared with 9.03±0.13 mm in the sedentary subjects. Furthermore, in the endurance-trained subjects, the femoral artery intima-media thickness was 4.6±0.1 mm compared with 4.7±0.1 mm in the sedentary subjects. These end points are considered important for assessing the integrity of the cardiovascular system. The large diameter of the arterial lumen plays a significant role in minimizing resistance against blood flow and maximizing perfusion to organs, tissues and cells.

In a study using rats, Kleim et al (17) found that exercise induces angiogenesis. Angiogenesis was evident by the increased blood vessel density in the area of muscle measured in the caudal forelimb area. In physically active rats, the blood vessel density in the caudal forelimb area was over 500 blood vessels/mm^2, whereas in inactive rats, the blood vessel density was less than 100 blood vessels/mm^2. The results showed that angiogenesis in the exercised parts facilitated better oxygen transport, reduced diffusion time and improved glucose uptake by the tissues. Through prolonged exercise over a 30 day period, the rats ran an average of 58.3 km, with the distance being increased on a daily basis. It was found that angiogenisis greatly benefited the musculoskeletal system and enhanced the functioning of the cardiovascular system in the rats.

A study conducted by Laufs et al (21) examined a group of male mice that were randomly divided into either a physically active group or a sedentary group. The exercise entailed voluntarily running a distance maintained on a running wheel (a wheel was provided to each of the physically active mice). This study used the fact that vascular function not only depends on endothelial cells, but also is affected by circulating EPCs derived from the bone marrow. The results revealed that physical activity elevates a particular subset of bone marrow-derived EPCs. These effects enhanced neoangiogenesis in the physically active group compared with the sedentary control group. As opposed to the controls, the plasma concentrations of circulating EPCs in trained mice were increased by 267±19%, 289±22% and 280±25% after seven, 14 and 28 days, respectively ($P<0.005$). Other advantageous effects of exercise were also noticed regarding neointima formation, lumen circumference and area of neoangiogenesis. These vascular angiogenic effects propagated by physical activity lend additional support to the hypothesis that exercise is tremendously beneficial for the cardiovascular system.

In summary, the limited data obtained from both animal and human studies indicate that physical activity plays a positive role in manifesting useful changes linked to vascular remodelling. Following exercise, the cardiovascular system benefits from increased angiogenesis, vasculogenesis and arteriogenesis. The theoretical foundation of vascular remodelling, accompanied by experimental evidence, shows a very promising approach for treating vascular ischemic diseases with exercise. Considering the positive influence of exercise on vascular remodelling, Lewis et al (22) have proposed gene therapy interventions that result in the upregulation of angiogenic factors. From the findings of animal and human studies, it appears sensible to promote the use of daily physical activity in all age groups by implementing public health policies that advocate an active lifestyle.

Influence of exercise on BP

When considering the positive impact of exercise on the cardiovascular system, BP and heart rate measurements are part of the package. Quantitatively, BP (systolic/diastolic) is directly proportional to blood volume and vascular resistance. Vascular resistance is largely controlled by the neuroendocrine system, which produces various hormones that cause vasoconstriction or vasodilation of the blood vessels (eg, catecholamines, cortisol, thyroid-stimulating hormone, angiotensin and endothelin). Some hormones (eg, aldosterone, renin and adrenocorticotropic hormone) influence BP by altering the blood volume or by modifying the glomerular filtration rate. Other hormones can influence BP by altering urinary flow rate and electrolyte disposal. The more constricted or narrow a blood vessel becomes, the greater the resistance produced on blood flow, consequently resulting in high BP. Readings of 120/80 mmHg are considered normal BP. However, if BP readings consistently exceed these values and remain around 140/90 mmHg, a person is considered to have hypertension. Blood volume is an important factor affecting BP, ie, the larger the blood volume, the more blood the heart has to pump, and this action increases the workload on the heart. The average blood volume of a human is approximately 8% of body weight, and this translates into approximately 5.6 L in a 70 kg man (35). When vascular resistance and/or blood volume decrease, BP proportionally declines (32).

To understand the effects of physical activity on BP, it is important to measure both systolic and diastolic BP. Systolic BP is determined by the arterial pressure exerted when the heart is contracting or emptying, whereas diastolic BP is determined by the pressure exerted on the arterial walls when the heart is relaxing or filling. Under stressful or vigorous exercise, the oxygen demand of the heart increases and, as a result, cardiac output and stroke volume increase, thus causing BP to increase as well.

The results of four studies (27-30) that assessed the effects of exercise on BP are summarized in Table 1. The data show that regular physical activity has a positive impact on lowering BP in hypertensive patients. All studies found consistent overall reductions in BP with the adoption of physical activity regimens. For instance, Rowland (28) found that in comparison with normotensive subjects, systolic BP was decreased by up to 8 mmHg and diastolic BP was decreased by up to 6 mmHg with the adoption of physical activity in hypertensive patients. Younger and older subjects who tended to have sedentary lifestyles risked an increase in BP over time, whereas those who

TABLE 1
Effects of physical activity on blood pressure (BP)

Type of exercise and duration	Subjects (n)	Change in BP	Reference
Routine exercise: daily throughout lifetime	Adults (1076)	Systolic BP ↓ by 8 mmHg in hypertensive patients; Diastolic BP ↓ by 6 mmHg in hypertensive patients; Systolic BP ↓ by 4 mmHg in normotensive subjects; Diastolic BP ↓ by 3 mmHg in normotensive subjects	28
Routine exercise: rehabilitation program – 6 months, 3 sessions, exercise to near maximal claudication pain	Older adults, 54–84 years (48)	Systolic BP ↓ significantly from 139±4 mmHg to 131±3 mmHg (P<0.05). No significant difference was found in diastolic values	30
Routine exercise: varying intensities Sedentary: 0 kcal/week Low: 1–999 kcal/week Moderate: 1000–1999 kcal/week High: >2000 kcal/week	Young and middle-aged men, 28–65 years (198)	Effects on systolic BP were not considered significant; however, those with physical activity either maintained or ↓ their systolic BP. The sedentary group's systolic BP ↑ from 122±13 mmHg to 124±16 mmHg. In sedentary people, diastolic BP dramatically ↑ from 81±9 mmHg to 83±9 mmHg. All other types of activity exhibited a marked ↓ in diastolic BP (P=0.03)	27
Routine exercise: frequency compared with sedentary habits of television viewing (<2 h/day to >4 h/day)	Middle-aged and older adults, 45–74 years (15,515)	As the duration of television viewing ↑, systolic/diastolic BP ↑ from 135.0/83.2 mmHg to 138.4/85.6 mmHg (P<0.001). As the level of vigorous activity ↑, both systolic and diastolic BP ↓. Combination had a compounding effect: vigorous activity with lowest level of television viewing led to lowest diastolic BP (82.25 mmHg in men and 78.5 mmHg in women)	29

↓ *Decreased;* ↑ *Increased*

were physically active seemed to evade this adverse effect. These findings strongly advocate the need for moderate daily physical activity to prevent hypertension.

Which component of BP (diastolic or systolic) is most affected by physical activity remains to be established. In general, the lower a person's resting BP is, the healthier his or her cardiovascular system should be, causing less wear and tear on the walls of the arteries. On the other hand, high BP is an important risk factor for inducing cardiovascular disorders, because hypertension increases the risk of cardiac ischemia and renal disease (16).

Effect of exercise on blood lipid profiles

Blood electrolytes, lipoproteins, total lipids and cellular constituents play a pivotal role in maintaining cardiovascular health. With regard to vascular plaque formation and BP, blood lipid profiles are of major interest. The lipids that are most easily and routinely measured are high density lipoprotein (HDL), low density lipoprotein (LDL) and total cholesterol. HDL and LDL differ mainly in function and composition. LDL, also known as bad cholesterol, has a much higher triglyceride component than does HDL, also called good cholesterol. On the other hand, HDL has a much higher protein content, lending to its higher density. LDL is the type of cholesterol that gets deposited in arterial blood vessels and, when floating freely in the vascular system, it tends to have its highest atherogenicity. The oxidation of LDL within blood vessels is considered to trigger the atherogenic process. HDL, however, acts as a 'scavenger', collecting excess LDL that has been deposited in the vascular tissue, which is then carried back to the liver for metabolic degradation (36). Maintaining balanced blood lipid profiles is clinically important in minimizing the formation of arterial blood vessel plaques and thrombi. Many studies have attempted to show the effects of exercise on blood lipid profiles, and the results of these studies are shown in Table 2 (25-27,30).

As can be seen from the results summarized in Table 2, routine physical activity (three to five days per week) markedly lowers the amount of LDL cholesterol (LDL-C) (up to 10 mg/dL) and increases HDL cholesterol (HDL-C) (up to 4.0 mg/dL), and exhibits a predominantly positive effect on blood lipid concentrations. Significant reductions in overall cholesterol and LDL-C, as well as increases in HDL-C, are known to have a positive impact on cardiovascular health.

Adverse effects of vigorous exercise

Despite all the obvious advantages of regular physical activity, there are some potential pitfalls if regimens are not properly integrated into a person's life. Sudden death from cardiac exertion may occur during or immediately after vigorous physical activity. For the most part, spontaneous death may not be directly related to sudden bouts of exercise but may instead be due to some other underlying cardiovascular impediment. Maron (37) found that sudden cardiac arrest is even more baffling when it occurs in well-trained athletes. However, the majority of these athletes had a pre-existing electromechanical or structural heart disease, most commonly associated with atherosclerotic coronary artery disease (CAD). In view of these serious outcomes, it can be inferred that moderate exercise may be the most desirable activity, because it is not necessary that physical activity be of high intensity to elicit the same health benefits (38). Furthermore, pushing people to perform vigorous exercise may have a negative impact on health promotion programs and on a person's health, increasing the incidence of drop-out and thereby preventing people from experiencing the health benefits so clearly provided by regular moderate physical activity, such as walking, bike riding, rowing and using treadmills.

TABLE 2
Effects of physical activity on blood lipid profiles

Type of exercise and duration	Subjects (n)	Change in lipid profile	Reference
Routine exercise: varying intensity Sedentary: 0 kcal/week Low: 1–999 kcal/week Moderate:1000–1999 kcal/week High: >2000 kcal/week	Young and middle-aged men, 28–65 years (198)	Physical activity >2000 kcal/week was associated with ↑ HDL concentrations. In the high-activity group, HDL levels ↑ by 0.05±0.19 mmol/L, whereas all other physical activities either were maintained or caused a ↓ in HDL concentrations	27
Routine exercise: rehabilitation program – 6 months, 3 sessions, exercise to near maximal claudication pain	Older adults, 54–84 years (48)	No significant effects were found on HDL concentrations. A significant ↓ was found in LDL-C concentrations from 123±4 mg/dL to 113±4 mg/dL. Total cholesterol levels also ↓ from 193±4 mg/dL to 183±4 mg/dL	30
Routine exercise: varying frequency for 24 weeks			26
Group 1: low-frequency walk, 3 days/week for 30 min to reach 50% target heart rate	Young and middle-aged Mexican women, 18–45 years (36)	Mean total cholesterol ↓ by 9 mg/dL; Mean LDL-C ↓ by 9 mg/dL; Mean HDL-C ↑ by 4 mg/dL	
Group 2: high-frequency walk, 5 days/week for 30 min to reach 50% target heart rate		Higher drop-out rate was observed; Mean total cholesterol ↑ by 3 mg/dL; Mean LDL-C ↑ by 6 mg/dL; Mean HDL-C ↓ by 4 mg/dL	
Routine exercise: rehabilitation program 4-month exercise training program: walking 60 min to 90 min, 5 to 7 days/week at 50% to 60% peak VO_2	Older adults, 52–72 years (15)	Tryglycerides ↓ markedly from 232.7±116.0 mg/dL to 177.5±56.2 mg/dL (P=0.02). HDL-C ↑ from 34.1±11.8 mg/dL to 36.4±7.4 mg/dL (P=0.08). The ratio of total cholesterol to HDL-C significantly ↓ from 5.6±0.9 to 4.8±1.3 (P=0.02)	25

↓ Decreased; ↑ Increased; HDL-C High density lipoprotein cholesterol; LDL-C Low density lipoprotein cholesterol; VO_2 Oxygen consumption

Generally, routine exercise of varying frequency and intensity is recommended in rehabilitation programs. However, even low-intensity exercise may not be advisable for patients with chronic heart failure. If a patient has chronic heart failure or has experienced a heart attack or stroke during the past six months, he or she must seek a doctor's advice before undertaking routine exercise of any intensity.

DIET-BASED BENEFITS FOR CVD

"You are what you eat" is a common expression. This quote epitomizes the importance of consuming a balanced healthy diet to ensure overall well-being. Orally taken food undergoes various digestive and metabolic processes, and is either used as a source of immediate energy or stored in the body for later use. In humans, the macronutrient foods that can be used for energy or storage in the body are carbohydrates, proteins and fats. Vitamins and trace elements, known as micronutrients, act as cofactors and play a pivotal role in intermediary metabolism and energy extraction processes. To meet the body's growth and daily energy demands, a properly balanced macronutrient and micronutrient diet is essential. The maintenance of nutrient balance is also required for protection against infectious diseases and the preservation of physiological homeostasis.

Type 2 diabetes is a chronic disease that is consistently linked with the development of CVDs. To minimize diabetes-associated health risks, the diet can be altered to allow diabetic patients to more easily cope with their diminished metabolic capacities (39). Specifically, to offset the development of CVDs and other metabolic disorders in type 2 diabetic patients, the following dietary adaptations can be made: reductions in caloric intake (by 500 kcal/day to 800 kcal/day), total fat intake (especially saturated fat) and food portion sizes; increased consumption of dietary fibre; and moderate alcohol use (40). Davis et al (41) reported that a well-balanced diet with a reduced glycemic load may lower the risk of obesity and type 2 diabetes. This inference was drawn from a two-year study performed in 179 subjects (81 men and 98 women) over 65 years of age. The participants were divided into two dietary groups with varying glycemic loads. The men and women in the lower glycemic load cluster consumed diets with a glycemic index of 113.7±44.2 and 94.0±27.5, respectively. On the other hand, the men and women in the higher glycemic load cluster consumed diets with glycemic indices of 139.9±38.8 and 110.7±35.9, respectively (P<0.01). The mean glycemic index for the entire sample was 115.6±39.9. Participants with a lower glycemic load consumed more carbohydrates from cereal, fruits, vegetables and milk, whereas those with a higher glycemic load consumed more breads and desserts. The results showed that, as opposed to the nutrient-dense carbohydrate foods, the lower glycemic load foods were highly useful in reducing the risks of diabetes mellitus, obesity and many chronic diseases in the elderly population.

There is an abundant amount of evidence to suggest that diets rich in fruits, vegetables, whole grain breads, high fibre cereals, fish, low-fat dairy products and diets low in saturated fats and sodium, can markedly reduce the risk of developing obesity and CVDs. However, the prioritization of taste and convenience in Western society hinders our ability to consume 'heart healthy' diets. Research has also shown that, although people in the West do not generally follow these healthy eating habits, other nationalities (eg, Mediterranean nations) have been able to adopt heart healthy dietary standards (42). Considering the potential benefits of the Mediterranean diet, it is suggested that North Americans and Europeans should also consider consuming such diets.

It has been almost 50 years since Ancel Keys (43) compared the rates of heart disease and the diets in seven countries (ie, Greece, Italy, Yugoslavia, Finland, Japan, the Netherlands and the United States). His work was a scientific cornerstone that showed the health advantages of the Mediterranean diet, which consists of whole grains, fruits, vegetables, nuts and olive oil. On the basis of his studies, Keys proposed that the plant-based diet of the people of the Mediterranean region offered protection against heart disease. Since that time, innumerable studies have been conducted to investigate the influence of dietary patterns and their ability to protect against a growing list of chronic diseases, including CAD and other CVDs, diabetes mellitus, and prostate and colon cancer, as well as some other cancers. Recent investigations have provided additional evidence that it is time to abandon the fixation with 'low-carb' diets and opt instead for the Mediterranean-type diet.

Recently, two studies dealing with the Mediterranean diet and lifestyle factors were published by Knoops et al (44) and Esposito et al (45). The first study (44) was performed with more than 2000 elderly men and women (70 to 90 years of age) in 11 European countries. This study assessed the effects of a Mediterranean-type diet and several lifestyle factors on the 10-year mortality from all causes, including CVDs and cancer. Besides the diet, other lifestyle factors examined were physical activity (approximately 30 min exercise per day), moderate alcohol use and whether the subjects smoked. Adhering to the Mediterranean diet was associated with a 23% lower risk of death from all causes. Those who consumed moderate amounts of alcohol had a 22% lower mortality risk, whereas being physically active resulted in a 37% decreased mortality risk. Being a nonsmoker decreased the risk of dying by 35%. Overall, those subjects who fell into all four categories had a remarkable 65% reduced death rate during the 10 years. While this study examined death rates, numerous other investigators have dealt with the reduction of chronic disease conditions and improvements in the quality of life with the Mediterranean-type diet and healthy lifestyles (46-68).

The second study (45) evaluated the effects of the Mediterranean-type diet on a cluster of risk factors for a condition known as metabolic syndrome. Risk factors that contribute to metabolic syndrome include obesity or excess fat around the abdomen, high BP, abnormal blood cholesterol and glucose intolerance. Metabolic syndrome usually goes hand-in-hand with a host of risk factors for CVD and stroke, diabetes and some forms of cancer. The results of this study provided additional evidence on how to stay healthy and free of heart attack and stroke.

In the metabolic syndrome study (45), 180 patients (99 men and 81 women) were placed on two different diets: one group was given a Mediterranean-type diet (n=90) and the other group received a lower-fat heart healthy diet (n=90). Patients on the Mediterranean diet were also advised on how to increase their daily consumption of whole grains, vegetables, fruits, nuts and olive oil. All patients were followed up for up to a two-year period. In comparison with the lower-fat dietary group, patients on the Mediterranean diet had significant reductions in body weight (–4.0 kg versus –1.2 kg, P<0.001), systolic BP (–4.0 mmHg versus –1.0 mmHg, P=0.01), diastolic BP (–3.0 mmHg versus –1.0 mmHg, P=0.03), blood sugar readings (–8.0 mg/dL versus –2.0 mg/dL, P<0.001) and blood insulin concentrations (–4.0 μU/mL versus –0.5 μU/mL, P=0.01). In addition, a decrease was found in their blood cholesterol (–11.0 mg/dL versus –2.0 mg/dL, P=0.02) and triglyceride concentrations (–18.0 mg/dL versus +1.0 mg/dL, P=0.001). At the same time, their HDL-C was increased (+4.0 mg/dL versus +1.0 mg/dL, P=0.03). Compared with subjects on the lower-fat diet, those on the Mediterranean diet had improved endothelial function, which was indicative of decreased inflammation of the arteries and a potentially reduced risk of heart attack and stroke. By the end of the study, approximately one-half of the subjects on the Mediterranean diet no longer had the typical markers of metabolic syndrome, whereas subjects taking the lower-fat diet did not have any significant clinical improvements.

It is worth noting that the overall health benefits observed from the above mentioned studies occurred not due to the Mediterranean diet per se, but because of the combination of several other factors such as active lifestyle, nonsmoking and moderate use of alcohol. Numerous other dietary intervention studies (46-68) have shown relationships between cardiovascular health and a balanced diet . Collectively, the results of all these studies suggest that promotion of an active lifestyle and the choice of healthy food and dietary habits may provide a powerful weapon against the morbidity and mortality associated with CVDs and other chronic diseases worldwide.

Role of dietary fat in cardiovascular health and disease

For several decades, there has been controversy about the involvement of dietary fat and fatty acids in the occurrence of CVD. Most often, people were made to believe by dieticians that all fats were bad and their use should be kept at a minimum level. However, this 'fear of fats' has been abated and the public is now being informed of the advantages of 'good fats' and the deleterious effects of 'bad fats'. For example, monounsaturated fats, polyunsaturated fats, plant sterols and essential fatty acids are categorized as good fats. On the other hand, saturated fats and trans fatty acids are categorized as bad fats.

Physiologically, lipids play an important role in the proper functioning of the cardiovascular system (69-71). Although the heart is fuelled in part by glucose and lactate, it predominantly and preferentially uses fatty acids to meet its energy needs. During starvation, up to 90% of the energy demands of the heart are fulfilled by fatty acids. During a fasting state, carbohydrates provide 15% to 20% of the energy requirements, divided between glucose (approximately 5%) and lactate (approximately 10%). The remaining energy provided by lipids is divided between triglycerides (approximately 10%) and free fatty acids (approximately 60%) (66-68). Therefore, the idea of eliminating fats from a heart healthy diet is simply preposterous. Instead, the idea of maintaining a proper balance and appropriate ratios of fats in the diet must be stressed, thus allowing for the proper functioning of the cardiovascular system. Some recently published findings regarding the role of fat and fatty acids in the cardiovascular system and overall health are discussed below.

Due to the presence monounsaturated fat in olive oil, it has been suggested that consuming approximately two tablespoons (approximately 23 g) of olive oil daily may reduce the risk of CAD. On November 1, 2004, the United States Food and Drug Administration allowed for a health claim on labels of olive oil and olive oil-containing foods that olive oil consumption decreases the risk of CAD in both men and women. According to the Food and Drug Administration, these labelling changes on olive oil products would help consumers to make more informed decisions about maintaining healthy dietary practices,

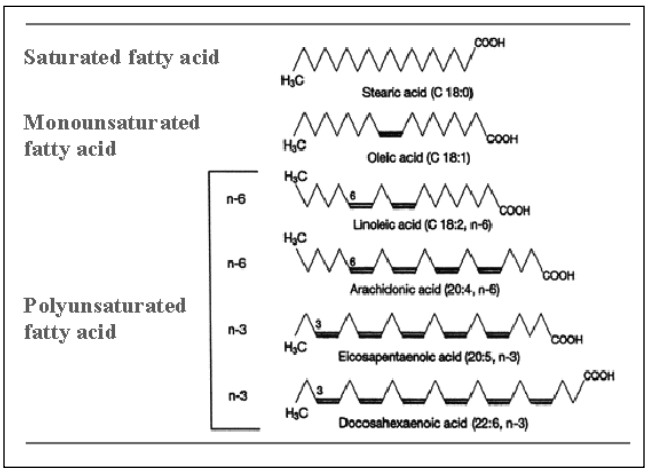

Figure 2) *Chemical structures of different fatty acids. Saturated fats contain no double bonds, monounsaturated fats contain one double bond and polyunsaturated fats contain two or more double bonds. Saturated fats tend to be solid at room temperature, whereas monounsaturated and polyunsaturated fats tend to be liquid at room temperature (128)*

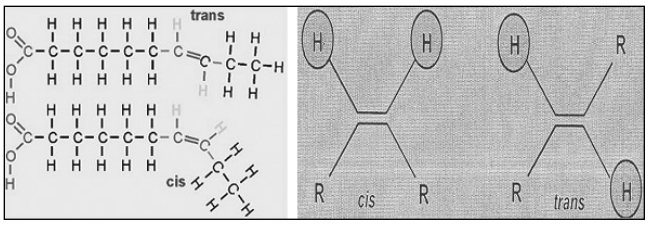

Figure 3) *Chemical structural differences between cis and trans fatty acids. Trans fatty acids rarely occur in nature, but are produced as a result of hydrogenation and fermentation, processes that saturate double bonds. The trans fats are hard for the body to metabolize and are responsible for causing atherosclerosis, heart disease, diabetes and obesity (36)*

while at the same time not increasing the total number of calories consumed daily (72).

Saturated, monounsaturated and polyunsaturated fats (Figure 2) differ in their physicochemical properties and physiological function. Chemically, saturated fats contain no double bonds, whereas monounsaturated fats contain one double bond and polyunsaturated fats contain more than one double bond (50). The 'diet-heart' hypothesis, initially proposed by Anitschkow, states that saturated fats have deleterious effects, whereas polyunsaturated fats produce beneficial effects on health (68). To date, the diet-heart hypothesis continues to gain support from experimental and clinical studies.

Recently, saturated fats and trans fatty acids have come under scrutiny as likely culprits in the manifestation of CVD. Trans fatty acids (Figure 3) are those fatty acids that are made to undergo a chemical process known as hydrogenation, wherein hydrogen atoms are added to break double bonds in the fatty acid chain. This hydrogenation process saturates the fatty acids. Previously, hydrogenation was commonly used to harden soft margarine, until it was discovered that an isomeric *trans* configuration of the hydrogen atoms resulted from this process. Trans fats are found in highly processed foods such as doughnuts, cookies and crackers. The synthetically produced trans configurations of fatty acids are not naturally found in the body and may cause deleterious effects, especially in the cardiovascular system. The body is unable to process trans fats and, as a result, they have been associated with increased risk of atherosclerosis and CVD (45). The exact mechanism of action of saturated and trans fats in the development of heart disease is unclear, but various theories have been proposed. Physiologically, trans fats act more like saturated fats, which tend to block LDL receptors, thus preventing their uptake from the bloodstream. These circulating LDLs may then be oxidized and lay the foundation for atherosclerotic plaques. The unnatural configuration of trans fats makes them much less soluble and reduces their packing ability. As such, they tend to cause more damage within arterial blood vessels. In addition, high consumption of trans fats is said to increase blood concentrations of lipoprotein (a) (50). Elevated plasma concentrations of lipoprotein (a) are considered to increase the risk of developing atherosclerosis, and the lipoprotein (a) complex mimics certain growth and clotting factors, thereby accelerating atherosclerosis. Once a correlation between trans fats and CVD was shown, a new process of using plant sterols in margarine was adopted, and this seems to play a positive role in maintaining cardiovascular health. As a result of the documented adverse effects, Denmark banned the use of trans fatty acids a few years ago. Canada has since followed suit, enacting legislation in the fall of 2004 that curtailed the consumption (8.5 g/day) of trans fats among Canadians (73).

The relative ratio in which different dietary fats are consumed is closely linked to blood lipid concentrations. Depending on the forms of dietary fat consumed, blood concentrations of HDL and LDL are affected. As stated earlier, high LDL and low HDL plasma concentrations are considered to cause deleterious effects on the cardiovascular system, whereas increased HDL and decreased LDL concentrations have cardioprotective effects (65).

In a systematic review of 27 studies (30,902 person-years of observation), Hooper et al (48) assessed the effects of dietary fat intake and prevention of CVD. Their meta-analysis included data from randomized placebo-controlled clinical trials of at least six month to two year duration. The dietary trials included any of the following interventions: reductions in the intake of total fat, saturated fat and dietary cholesterol, or a change from saturated to unsaturated fat. The results showed that cardiovascular mortality was reduced by 9% and cardiovascular events (eg, MI, stroke and peripheral vascular events) by 16% with reduction or modification of dietary fat intake. In comparison with the six-month trials, data from two-year follow-up trials provided stronger evidence of protection from cardiovascular mortality and morbidity after the modification or decreased intake of dietary fat or cholesterol.

Up to a 24% reduction in cardiovascular events was observed in randomized placebo-controlled dietary fat trials lasting over two years. Based on the meta-analysis of well-designed clinical trials, it appears that significant reductions in CVDs can be achieved by continuous reduced intake of dietary fat and cholesterol, or by modifying the proportions of dietary fat and cholesterol intake.

Paradis and Fodor (68) reviewed the effects of different dietary fats on blood lipid concentrations. It was found that saturated fats increased both LDL and HDL plasma concentrations. Replacing the saturated fats with polyunsaturated fatty acids seemed to counteract the negative effects associated with the saturated fats. The polyunsaturated fats reduced LDL concentrations, but had no apparent effect on HDL concentrations. The

consumption of omega-3 fatty acids and fish oils seemed to be cardioprotective. The fish oils lowered triglyceride concentrations, platelet aggregation and BP, thereby suggesting multiple beneficial effects on cardiovascular health. Replacement of saturated dietary fat with monounsaturated fats also provided beneficial effects to the cardiovascular system by lowering LDL concentrations. Although the mechanistic actions of monounsaturated fats on HDL concentrations remain unclear, trans fatty acids have been shown to have deleterious effects on the cardiovascular system. Once again, the findings of the above mentioned studies indicate that saturated fat and trans fatty acid consumption should be kept to a minimum. On the other hand, increased consumption of monounsaturated and polyunsaturated fats (eg, fish oils and olive oil) should become an important part of a dietary strategy for reducing the risk of CVD in not only individual people but in populations at large.

In a large questionnaire-based study examining 80,082 women aged 34 to 59 years, Hu et al (49) determined the effects of various dietary fats on CAD risk. Fat content was measured and reported according to the frequency of consumption of a particular dietary component, namely, trans isomers of 18-carbon unsaturated fatty acids and polyunsaturated linoleic acid. The subjects were followed up for 14 years beginning in 1980. Saturated fats and trans fatty acids clearly increased the relative risk associated with CAD. On the other hand, increased consumption of monounsaturated and polyunsaturated fats resulted in decreased risk of CVD. The incidence of cardiovascular events was decreased by 42% with a 5% reduction in saturated fats, which were then replaced with unsaturated fats. In addition, replacing a mere 2% of trans fats in the diet with unsaturated fats led to a 53% reduced risk of CAD. These findings strongly support the diet-heart hypothesis, and indicate that saturated and trans fats are 'bad', whereas monounsaturated and polyunsaturated fats are 'good' for cardiovascular health.

By using assimilated data from controlled clinical trials, and restricting the use of saturated and trans fats, Katan (47) proposed dietary replacements for saturated and trans fats. He suggested the use of carbohydrates, proteins, monounsaturated fats and polyunsaturated fats (eg, linoleic acid) as substitutions for saturated and trans fats in the diet. Numerous studies have indicated that polyunsaturated fats are the most effective means of reducing blood cholesterol concentrations, especially LDL. Dietary interventions with carbohydrates and monounsaturated fats also decrease HDL concentrations, thus counteracting the benefits seen with decreased LDL concentrations. Replacing saturated fats with high protein avoids the decline in HDL concentrations and increase in very low density lipoprotein concentrations. However, the high protein diet may increase the risks of osteoporotic fracture and kidney damage.

To determine the cardioprotective potential of the omega-3 polyunsaturated fatty acids contained in fish oil, Toft et al (46) conducted a randomized double-blind placebo-controlled study in 78 subjects with untreated hypertension for 16 weeks. The treatment group received fish oil (4.0 g/day) and the placebo group received corn oil (4.0 g/day). The activities of plasma PAI-1 and t-PA, the concentrations of fibrinogen and factor VIIc, and the platelet count were measured before and after the dietary intervention. All of these variables remained unchanged from pretreatment levels during fish oil intake, except fibrinogen concentrations, which significantly increased with both fish oil (0.6±0.1 g/L, P=0.0001) and corn oil (0.4±0.1 g/L, P=0.002) treatment. High fibrinogen concentrations are known to increase the risk of clot formation. The findings of this investigation suggest that coagulation risk due to elevated fibrinogen was virtually the same for both fish oil and corn oil treatment. It was concluded that the daily intake of 4.0 g of omega-3 polyunsaturated fatty acids does not modify the activities of PAI-1 and t-PA in hypertensive patients. Hypertension has been associated with elevated PAI-1 activity and the subsequent development of thrombosis and MIs. Dietary supplementation with fish oil may be helpful in the slowing of atherosclerosis, but may have limited effects in the prevention of heart attack and stroke. The results of this study also showed that fish oil helps to reduce plasma triglyceride concentrations.

Other lipids that seem to lower the risk of CVDs are plant sterols (phytosterols) and stanols. Phytosterols are composed of steroid rings and are different from triglycerides and phospholipids. Although plants do not contain cholesterol, phytosterols have a similar function and structure. Physiologically, some types of plant sterols seem to act like cholesterol in the human body and compete with cholesterol for uptake and metabolism by the cells (45). In doing so, phytosterols reduce blood LDL concentrations without affecting HDL (51). In a randomized double-blind placebo-controlled study (n=100), Weststrate and Meijer (52) found that the consumption of phytosterol-enriched margarine (30 g/day for four consecutive 24 to 25 day periods) reduced plasma LDL concentrations by 8% to 13%. These results suggest that phytosterol intake may reduce the risk of developing atherosclerosis and may help to combat CVD.

The information gathered from published studies indicates that it is extremely important to choose the quality and quantity of fats, because their dietary proportions have a large impact on cardiovascular health and disease. People should be encouraged to follow dietary reference intakes set by regulatory health authorities. Dietary reference intakes recommend that fat should form approximately 20% to 35% of the daily energy intake, with essential fatty acids (ie, omega-3 and omega-6) being included as part of a heart-conscious diet (74). Current evidence suggests that the amount and proportion of essential fatty acid consumption is much lower than recommended, and has deviated greatly from intake levels during the early evolutionary stages of humans. It has been observed that among various ethnic groups, the Indo-Canadian population is at a relatively high risk of CVDs and diabetes mellitus (75). This may be attributed to the high use of butter fat and fried foods consumed in Indian households. Although the Indian diet is low in total fat, it has a high omega-6 to omega-3 ratio (38:1), which may be associated with a greater risk of atherosclerosis and obesity. It has been suggested that changing the cooking oils and increasing the intake of fruits and vegetables in the diet would bring down the omega-6 to omega-3 ratio, resulting in reduced CVD mortality and prevention of obesity and diabetes (75,76). Therefore, consumption of omega-6, omega-3, monounsaturated and polyunsaturated fats should be proportionally altered to compensate for unhealthy dietary habits. At the same time, people should minimize their intake of saturated and trans fats, while keeping in mind their atherogenic potential and, thereby, ensuring a positive impact of dietary lipids on cardiovascular health (77). Examples of omega-3 and omega-6 polyunsaturated fatty acids are shown in Figure 4.

Influence of sodium on CVD

Na^+ is a cation that plays an essential physiological role in maintaining blood volume and transmembrane potential in

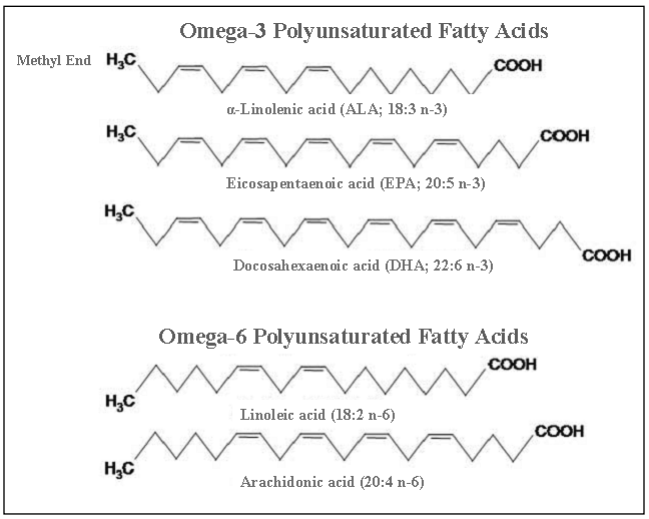

Figure 4) *Chemical structures of omega-3 and omega-6 polyunsaturated fatty acids*

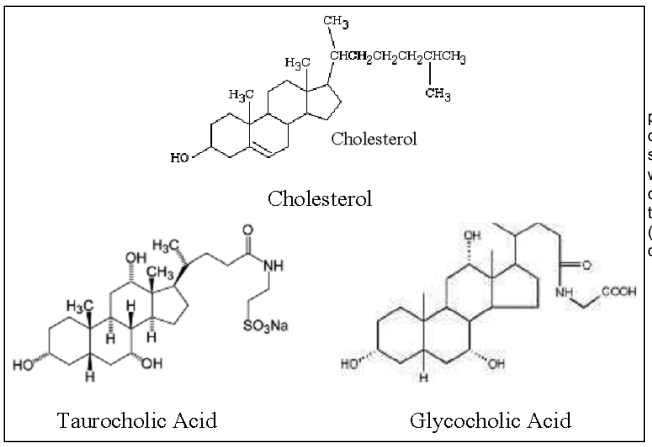

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Figure 5) *Potential mechanisms by which dietary fibre may help in lowering plasma cholesterol. Fibre has a trapping and adsorbing action, which causes bile salts (taurocholic acid and glycocholic acid) to adhere to the rigid network. Bile acids are produced from cholesterol. When bile salts are trapped by dietary fibres and excreted into the feces, more cholesterol stores are mobilized to produce bile acids. To enable this process, the liver takes up more lipids from the blood to replenish cholesterol stores. The de novo synthesis of bile acids reduces serum lipid concentrations, causing an overall beneficial effect on cardiovascular health*

cells. It is involved in regulating neural transmission and cardiorenal functions (78). With regard to the cardiovascular system, the excretion and reabsorption of Na^+ by the renal tubules directly affects blood volume and pressure. In humans, a large dietary source of sodium is table salt (NaCl).

A report by Graudal et al (58) suggests that a high consumption of NaCl increases BP. However, controversy still exists about sodium restriction, because reduced NaCl consumption results in increased LDL concentrations. Therefore, the antihypertensive action of restricted salt consumption may be cancelled out by increases in LDL concentrations.

Bray et al (57) assessed the effects of three dietary sodium levels on BP in 412 participants. This study incorporated graded declines in sodium intake (ie, 150 mmol/2100 kcal, 100 mmol/2100 kcal and 50 mmol/2100 kcal for 30 days) and observed respective reductions in BP with each sodium intake level. Their data showed that sodium-restricted diets had an antihypertensive effect in people who consumed a specialized diet, as well as in the controls who consumed a typical American diet; the significant reductions in BP observed were a mean reduction in systolic BP from 5 mmHg to 8 mmHg and a mean reduction of diastolic BP from 2 mmHg to 4 mmHg. It was concluded that monitoring sodium intake elicits a cardioprotective effect. One pitfall of this study, however, is that the investigators failed to look at the possible consequences regarding blood lipid concentrations, which may produce adverse effects on overall cardiovascular health.

Aviv (56) reported that excess NaCl intake may cause hypertension and adversely affect the cardiovascular system and kidneys in 'salt-sensitive' people. It has been shown that excess salt consumption increases the left ventricular mass and causes stiffness of the aorta. These adverse cardiovascular events suggest that caution should be exercised in choosing dietary sodium levels.

Because sodium plays an important role in normal physiological functions, salt restriction may not be a good strategy for normotensive people, whereas restriction may be beneficial in lowering BP in hypertensive patients (59). As with other minerals (eg, cobalt, zinc and potassium), it is important to maintain a mineral balance in the diet that ensures that normal sodium concentrations are not offset, inadvertently causing ill health effects.

Influence of dietary fibres on CVD

Although dietary fibres do not supply energy to the body, their dietary presence plays an important role in gastrointestinal function and cardiovascular health. There are two types of dietary fibres, namely, soluble (eg, pectins, some hemicelluloses, mucilages and gums) and insoluble (eg, cellulose and many hemicelluloses), each with varying physiological and pharmacological properties. Soluble fibres are gel forming and they help to lower blood cholesterol (specifically LDL) and the rate of glucose absorption from the intestine, thus preventing sudden spikes in blood sugar concentrations (considered ideal for diabetic patients). Insoluble fibres help in trapping a wide variety of materials, softening the stools and hastening peristaltic movements of the gastrointestinal tract. Fibres stimulate saliva production in the mouth and the lubrication of food. As food passes to the stomach, fibres give a feeling of fullness, displace high-fat foods from the diet and delay gastric emptying to permit optimal digestion and nutrient absorption. In the small intestine, fibres dilute the contents and delay absorption of dietary fat, cholesterol and glucose. Bile salts (eg, glycocholate and taurocholate) and minerals may also be adsorbed and trapped on the fibres. The trapping or adsorption by fibres has a direct effect on cholesterol absorption and metabolism.

Cholesterol is the precursor of bile salts (Figure 5), which are synthesized in the liver, stored and concentrated in the gall bladder, and then released into the small intestine. Bile salts are involved in the emulsification of fat and make the lipids more readily absorbable by the intestine. The trapping of bile salts by dietary fibres impedes their enterohepatic circulation. Consequently, more cholesterol stores are mobilized in the body to produce bile salts. To accomplish this process, the liver takes up more lipids from the blood to replenish cholesterol stores. The de novo synthesis of bile acids from cholesterol coupled with decreased absorption of lipids from the intestine helps to lower plasma triglyceride concentrations and produce beneficial effects for the cardiovascular system. Fibre-induced trapping of minerals is only a problem in people with mineral-deficient diets (53,79).

In a randomized double-blind placebo-controlled trial evaluating 21,930 smoking men aged 50 to 69 years, Pietinen et al (55) found that fibre intake was inversely related to the risk of various cardiovascular events such as MI, CAD and coronary death. The results of this cohort study are summarized in Table 3. A statistically significant inverse relation was found between various forms of fibre and the relative risk of major coronary events; however, after intervening variables were taken into account, only the soluble fibre content of the diet significantly affected the relative risk of CAD. The relative risk of those with the highest soluble fibre content (7.4 g) was 0.83 compared with those consuming only 3.7 g of soluble fibre. With regard to coronary deaths, the effects of most types of dietary fibre were statistically significant, despite considering intervening factors such as age, intake of dietary supplements and other risk factors. After these modifications, the effect of vegetable and fruit fibres became nonsignificant. However, dietary fibre, soluble fibre, insoluble fibre, insoluble noncellulosic polysaccharides, lignins, cellulose and cereal fibre still had a statistically significant inverse correlation to coronary infarction-related death. According to Pietinen et al (55), even after considering the effects of various other intervening factors, dietary fibres still elicit protective effects on cardiovascular health, thereby reducing the relative risk of CVD and coronary deaths.

In another cohort study, Mozaffarian et al (54) examined 3588 men and women (65 years of age or older) from 1989 to 2000 to assess the effects of fruit and vegetable fibre intake on the risk of CVD. Fibre intake was split into quintiles to measure the effects on CVD risk. The highest quintile consumed 7.9 g/day cereal, 9.1 g/day of fruit and 11.7 g/day of vegetable fibre. The lowest quintile consumed 0.8 g/day, 1.7 g/day and 2.9 g/day of each of the respective fibres. After adjustments for intervening factors, the relative risk of CVD was significantly reduced with increased cereal fibre consumption. At the highest quintile of cereal fibre consumption, the relative risk associated with CVD was 0.79 compared with the lowest quintile (95% CI 0.62 to 0.99, P=0.02). The findings suggested that future recommendations should include increased consumption of dietary fibre without discrimination by age, because it seems that even the elderly population can benefit from the cardioprotective actions of dietary fibres.

Rimm et al (53) conducted a six-year cohort study from 1986 to 1992. Once again, this study evaluated the relationship between vegetable, fruit and cereal fibre intake and the risk of CAD (evaluated by using MI as the outcome measure). This study included 43,757 American men aged 45 to 75 years, who were split into groups based on the type of dietary fibre intake. The highest quintile consumed 28.9 g/day, whereas the lowest quintile consumed 12.4 g/day. A statistically significant inverse relationship was found between total dietary fibre intake, nonfatal MI, fatal coronary disease and total MI. The relative risk of nonfatal MI for those in the highest quintile was 0.65 (95% CI 0.49 to 0.88, P=0.02) compared with those in the lowest quintile of fibre intake. The relative risk of fatal coronary disease for those in the highest quintile was 0.45 (95% CI 0.28 to 0.72, P<0.001) compared with those in the lowest quintile. With regard to total MI, the relative risk of those in the highest quintile was 0.64 (95% CI 0.47 to 0.87, P=0.004) versus those in the lowest quintile of fibre consumption. When separated into the individual fibre categories, vegetable and cereal fibres still had a statistically significant inverse relationship between relative risk and total MIs. Those who were in the highest quintile (11.1 g/day) for vegetable fibre had a 0.83 relative risk (95% CI 0.64 to 1.08, P=0.05) compared with those in the lowest quintile (1.2 g/day). Cereal fibre had a large inverse relationship to relative risk associated with CAD, in which those consuming 9.7 g/day (highest quintile) had a 0.71 relative risk (95% CI 0.54 to 0.92, P=0.007) compared with the lowest quintile consuming 2.2 g/day.

TABLE 3
Dietary fibre intake and the relative risk of cardiovascular disease (CVD) in a cohort of Finnish men

Type of fibre	Amount of dietary fibre (g) (lowest vs highest)	Relative CVD risk (95% CI)	P
Dietary fibre	16.1 vs 34.8	0.73 (0.56–0.95)	0.004
Soluble fibre	3.7 vs 7.4	0.68 (0.50–0.92)	0.003
Insoluble fibre	12.2 vs 27.7	0.75 (0.58–0.98)	0.01
Insoluble NCP	6.8 vs 15.9	0.67 (0.52–0.88)	0.01
Lignin	2.1 vs 5.8	0.75 (0.58–0.97)	0.002
Cellulose	3.1 vs 6.3	0.72 (0.54–0.97)	0.006

NCP Noncellulosic polysaccharides; vs Versus. Data from reference 55

Altogether, the data of several epidemiological studies reveal an inverse relationship between dietary fibre consumption and CVD risks; that is, the greater the amount of dietary fibre consumed, the lower the risk of CVD. The underlying mechanism(s) for the prevention of CVD due to dietary fibre intake remains unknown, but the collective epidemiological evidence for CVD prevention is a compelling reason to recommend that dietary fibre consumption be encouraged for all ages. Insoluble and cereal fibres seem to have the most noticeable effects in combating various aspects of CVD, such as nonfatal MI and, more significantly, fatal coronary events.

Role of fruits, vegetables and antioxidants in the prevention of CVD

Fresh fruits and vegetables are essential components of the diet. They are the most nutrient-rich dietary sources, containing fibre, vitamins, trace elements and antioxidants, which are essential to maintaining physiological homeostasis. The Canadian Food Guide (80) recommends five to 10 servings of fruits and vegetables on a daily basis. However, according to Statistics Canada (81), 55.2% of all Canadians aged 12 years or older consume fewer than five servings of fruits and vegetables per day. Among these people, males seem particularly susceptible to the effects of a lack of fruits and vegetables in their diets (81). Liu (66) suggests that the health benefits of fruits and vegetables are derived from the additive or synergistic actions of phytochemicals. Scientific evidence indicates that the consumption of fruits, vegetables and antioxidants provides a protective barrier against various chronic diseases, including CVD. This evidence-based nutrition research provides a solid basis for recommending the daily consumption of fruits and vegetables to the general public for the prevention of obesity, diabetes and CVDs.

To determine the beneficial effects of fruit and vegetable intake in the prevention of CAD, Joshipura et al (61) conducted a cohort study that followed up 126,399 men and women (34 to 75 years of age) for over seven years. It was found that, like consumption of dietary fibre, increased consumption of all fruits and vegetables had a statistically significant

TABLE 4
Fruit and vegetable consumption and the relative risk of cardiovascular disease (CVD) in American adults

Aspect of CVD	Fruit and vegetable intake (times/day)	Relative CVD risk (95% CI)	P
Stroke incidence	<1 vs ≥3	0.73 (0.57–0.95)	0.01
Stroke mortality	<1 vs ≥3	0.58 (0.33–1.02)	0.05
CVD mortality	<1 vs ≥3	0.73 (0.58–0.92)	0.008
Ischemic heart disease mortality	<1 vs ≥3	0.76 (0.56–1.03)	0.07

vs Versus. Data from reference 64

inverse relationship to the relative risk of CAD. The most significant inverse relation was seen with increased consumption of green leafy vegetables. At the highest quintile (approximately 9.65 servings per day) of fruit and vegetable consumption, the relative risk of CAD was 0.80 (95% CI 0.69 to 0.93) compared with the lowest quintile (approximately 2.73 servings per day). In addition, the relative risk associated with the highest quintile (approximately 1.43 servings per day) of leafy green vegetable consumption was 0.72 (95% CI 0.63 to 0.83) compared with the lowest quintile (approximately 0.16 servings per day). This large cohort study confirmed the earlier observations of Joshipura et al (60) in which an inverse relationship was found between fruit and vegetable intake and the relative risk of ischemic stroke. Once again, the diverse protective nature of fruits and vegetables indicates that daily consumption of these dietary products is beneficial for cardiovascular health and for the prevention of chronic diseases.

Bazzano et al (64) conducted a long-term follow-up study for approximately 19 years to determine the effects of fruit and vegetable intake on the occurrence of CVD. This study, the results of which are summarized in Table 4, examined 9608 American adults aged 25 to 74 years. Of note, a strong inverse association was found between fruit and vegetable consumption and the risk of subsequent CVDs such as the incidence of stroke mortality and ischemic heart disease mortality. The results of this long-term study lend additional support to previous studies and clearly show that the daily consumption of fruits and vegetables reduces the incidence of morbidity and mortality related to CVDs.

The antioxidants contained in fresh fruits and vegetables have been shown to reduce the risk of CVDs and some forms of cancer. Clinical evidence indicates that antioxidants have the ability to slow the process of atherosclerosis by preventing the oxidation of LDLs. Oxidized LDLs seem to lay the foundation for endothelial arterial plaques and are regarded as a culprit in the development of CAD and stroke. Antioxidant deficiency may lead to oxidative stress, resulting in the production of free radicals that cause cell injury and tissue damage (82-84). Recently, information along this frontier has been appearing in the popular press. For example, on October 25, 2004, Mario Toneguzzi (85) reported in the *Ottawa Citizen* that cranberry juice has cholesterol-lowering capabilities. Additionally, many articles in the lay press suggest that the moderate consumption of alcohol is associated with increased HDL concentration in the blood. Some reports have also focused on the cardioprotective ability of red wine, whereas more current information indicates that moderate consumption of any type of alcohol (eg, beer, wine or whisky) reduces the risk of heart disease.

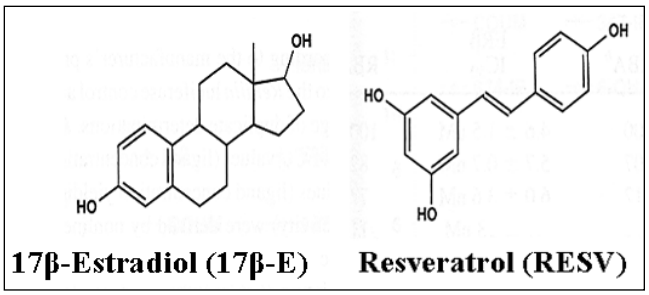

Figure 6) *Resveratrol (RESV) has some chemical resemblance to the ovarian hormone 17-beta-estradiol (17β-E). The structural resemblance between 17β-E and RESV may explain the mild estrogenic activity of the latter. Such estrogenic activity may be responsible for the cardioprotective action of RESV (67)*

Although red wine seems to contain certain unique antioxidant components (eg, phenolic substances and bioflavanoids [65]), an additional antioxidant compound found predominantly in red wine is known as resveratrol (86). This agent has a chemical structure resembling 17-beta-estradiol, the naturally produced ovarian estrogen (Figure 6). In vitro studies have shown that at small concentrations (1 μM to 10 μM), resveratrol acts as a mild estrogen agonist. The estrogen-like action of resveratrol may explain its cardioprotective nature and its ability to improve blood lipid profiles. However, at high concentrations (100 μM), resveratrol seems to exhibit antagonistic behaviours and may disrupt normal endocrine function. To verify the agonistic/antagonistic activities of resveratrol, in vitro studies (67,85) were conducted on human endometrial Ishikawa cells, which express human estrogen alpha and beta receptors.

As part of an average daily diet, people consume vitamins that are present as either fat or water soluble entities. These vitamins often act as coenzymes or catalysts that enable the proper functioning of metabolic pathways. Some vitamins (eg, vitamins A, C and E) have antioxidant potentials and help to minimize the tissue damage that results from a build-up of reactive oxygen species in the body. Vitamin A is most commonly consumed as an antioxidant in the form of β-carotene, whereas vitamin E is consumed in the form of α-tocopherol. For decades, water soluble vitamin C has been touted as an excellent immune booster and has been shown to aid in the respiratory burst necessary to combat a cold. However, on a more historical note, vitamin C that is consumed in combination with the amino acids L-lysine and L-proline at certain proportions was proposed as a cure for heart disease by the Nobel Laureate Linus Pauling and his associate Matthias Rath around 1971 (86). A study by Smith et al (87) showed the antioxidant actions of vitamin C on human aortic endothelial cells, suggesting a markedly reduced production of reactive oxygen species and reactive nitrogen species in human aortic endothelial cells ($P<0.05$) and in the mitochondria ($P<0.01$), as determined by fluorescence measurements. In addition to vitamins A and C, the antioxidant benefits of consuming vitamin E have also been shown. It has been reported (88,89) that vitamin E plays a crucial role in the initiation and propagation of atherosclerotic disease, and an adequate supply of vitamin E minimizes the degree of oxidative stress to which the body is constantly exposed.

Despite these seemingly positive cardioprotective effects, some studies warn about the dangers associated with antioxidant

TABLE 5
Overweight and obesity status corresponding to body mass index

Health status	Body mass index (kg/m^2)
Underweight	<18.5
Normal	18.5–24.9
Overweight	25.0–29.9
Obese	
Obesity class I	30.0–34.9
Obesity class II	35.0–39.9
Extremely obese	
Obesity class III	≥40.0

Data from references 92 and 93 and 97 to 99

vitamins, namely, an increased risk of CVD and all-cause mortality. For instance, a meta-analysis by Miller et al (90) showed that high doses of vitamin E (400 U/day or more) can increase all-cause mortality in humans. Although these findings were not statistically significant, a trend was apparent. Another study, conducted by Rapola et al (63), showed an increased incidence of major coronary events in men with a previous MI and who were taking supplements of α-tocopherol and β-carotene; of note, some men in this study were also smokers. Therefore, several confounding factors were present that may have contributed to their deaths. Waters et al (62) reported that antioxidant vitamin supplements by themselves or in conjunction with hormone replacement therapy, may increase the risk of coronary atherosclerosis in postmenopausal women. In this study, women in the treatment regimen were split into two groups: those with a hysterectomy were given 0.625 mg estrogen only, and those without a hysterectomy were given a combination of 0.625 mg estrogen plus 2.5 mg progesterone. In this experimental situation, the loss of estrogen may have contributed to the increased risk of CVD, because in menopausal women, the risk of CVD is similar to that in men. It is possible that the antioxidant vitamins were not responsible for the deleterious health effects experienced by menopausal women. Precautions should still be taken to avoid excessive use of antioxidant vitamin supplements by any age group. The majority of the literature supports the moderate use of antioxidants, because these dietary supplements may protect against chronic diseases such as cancer and CVD.

INFLUENCE OF OBESITY ON CVD

Obesity and the ills associated with it, including diabetes mellitus, heart disease and high BP, have joined the WHO's list of the top 10 global health problems. Obesity is a complex pathophysiological condition characterized by an excessive accumulation of body fat. It is a chronic disorder caused by a combination of genetic and environmental factors that determine the balance between caloric intake and expenditure. Excess body fat is associated with a significantly increased risk of morbidity and mortality, a reduced quality of life and increased health care costs. Obese people are more prone to metabolic syndrome, which is characterized by some distinctive abnormalities such as hypertension, dyslipidemia and insulin resistance in type 2 diabetic pateints. People with metabolic syndrome have a significant risk of developing type 2 diabetes, stroke and CAD.

Environmental factors such as diet and physical activity play an important role in the development of obesity, and this condition not only significantly increases the risk of diabetes, premature death and disability, but also is a fundamental determinant of heart disease and stroke. Obesity increases a person's number of unhealthy life-years, work disability, hospitalization due to CAD and need for long-term medication (91). Although there is a positive correlation between obesity and all-cause mortality, the specific evidence indicates an increased risk of chronic diseases such as type 2 diabetes, CAD, hypertension, stroke and some forms of cancer. Obviously, overweight and obese people are more prone to ill health and have an increased risk of developing several long-term health problems (92-95).

It is now well established that obesity is an important risk factor for type 2 diabetes and, in turn, uncontrolled diabetes mellitus promotes ischemic heart disease due to atherosclerosis. The results of the Framingham study (96) showed that the incidence of MI in patients with diabetes is two times greater in men and three times greater in women than in healthy people.

Obesity can be determined by taking various anthropometric measurements; however, body mass index (BMI), a ratio of body weight to height (kg/m^2), is considered the most accurate and well-defined value in determining obesity (97,98). According to clinical guidelines developed by expert panels (92,93,97-99), there are ranges of BMI that assign people into different health categories (Table 5). For example, a person with a BMI of 18.5 kg/m^2 to 24.9 kg/m^2 is considered normal or nonobese, whereas a person with a BMI of 25 kg/m^2 to 29.9 kg/m^2 is considered overweight, and a person with a BMI of 30 kg/m^2 or greater falls into the obese category.

Fat distribution is an important body composition characteristic to consider when dealing with obese people. Epidemiological and clinical evidence indicates that fat deposition in abdominal regions causes an increased CVD risk compared with gluteofemoral fat accumulation. In other words, persons with an 'apple-shaped' body are more prone to develop CVD than those with a 'pear-shaped' body. Thus, waist circumference is an important measurement to consider when assessing relative CVD risk. Men with a waist circumference greater than 102 cm (40 inches) and women with a waist circumference greater than 88 cm (35 inches) fall into a relatively high-risk group (93-95).

Although obesity does not discriminate between age and ethnicity, many people remain complacent about their risk of becoming obese. Adolescents are a key group that exhibits this invincibility complex, failing to realize that eating habits and lifestyle during these early years may lead to the development of atherosclerosis, MI and other chronic diseases later in life. This fact was shown in a study (100) that evaluated 1533 Portuguese children and adolescents aged eight to 12 years. In this study, 17.1% of subjects in the highest quartile of percentage body fat had twofold to threefold greater adverse risk factors (95% CI 1.3 to 3.2, P<0.005). The results indicated a strong correlation between childhood obesity and the risk of developing CVD or dying of CVD later in life.

Excess body fat increases the risk of mortality and morbidity in people with a prior history of CVD. Rana et al (101) showed this in a prospective study that examined 1898 patients who were hospitalized for MI. This study showed a correlation between obesity and the risk of all-cause mortality after MI; specifically, a graded risk was observed between BMI and MI, ie, as BMI increased, so did the corresponding risk of MI. When adjusting for compounding factors such as age, sex and

race, a statistically significant trend of MI was still observed (P=0.01). According to WHO standards, those who were overweight had a relative risk of 0.96, those with class I obesity had a relative risk of 1.44, and those with class II or III obesity had a relative risk of 1.62 for experiencing an MI compared with patients having a normal BMI. However, after accounting for other compounding factors (eg, age, sex, race, current smoking, former smoking, use of thrombolytic therapy, exertion, usual alcohol consumption, usual tea consumption, educational attainment and household income), the trend for MI was still apparent but no longer statistically significant. Collectively, these studies suggest that losing weight after cardiac events would not only prolong life but would also improve the quality of life for those living with CVD.

The definition of obesity has changed in various regions of the world. Studies have been conducted on subjects from the Asia-Pacific region, highlighting the importance of considering various genetic and environmental differences when classifying obesity. In the Asia-Pacific region, a BMI greater than 23.0 kg/m^2 is considered overweight and obesity begins at a BMI of 25.0 kg/m^2. Even at these lower BMIs, ill health effects are prevalent in this part of the world, including cardiovascular and metabolic adverse events as well as an overall decline in quality of life (102). A cohort study of 67,334 Chinese women aged 40 to 70 years attempted to show the relationship between various anthropometric measures and the relative risk of CAD (103). The results showed that with increasing gradation of BMI, parameters such as waist circumference, waist circumference to hip circumference ratio, waist circumference to standing height ratio, waist circumference to sitting height ratio and conicity were all statistically significant in increasing the relative risk of CAD. Compounding factors (ie, age, cigarette smoking, alcohol consumption, physical activity, level of education, family income, menopausal status, postmenopausal hormone use, oral contraceptive use, season of recruitment, and fat, dietary fibre and soy protein intake) were all accounted for while determining the relative risk of CAD (103).

Conservative estimates suggest that there are over one billion overweight people in the world, of whom at least 300 million are considered clinically obese (93,101). Recent statistics indicate that obesity has reached epidemic proportions globally, particularly among North American adults and children. These statistics are not difficult to fathom, considering that Americans consumed 69.9 kg of caloric sweeteners, 200.6 L of carbonated soft drinks and 90.7 kg of flour and cereal products per capita in 1997. Adverse dietary shifts, especially refined foods, have caused daily per capita caloric intakes to increase by 500 calories per day between 1970 and 1994 (75). These extra calories consumed remain unused due to the prevalence of sit-down jobs and the lack of physical activity, perpetuating a vicious cycle that leads to obesity.

Obesity is more prevalent among affluent societies, where this phenomenon is attributed to easy access to energy-dense foods and low levels of physical activity. In 2001, 58% of the American population was overweight. Moreover, between 1986 and 2000, obesity rates doubled from 10% to 20% and, at the same time, the prevalence of extremely obese people quadrupled from 0.5% to 2%. Epidemiological surveys conducted in 2001 indicated that the Canadian plight is not any better than in the United States. Close to one-half (47.4%) of Canadians are overweight, and the prevalence of clinical obesity is approximately 14.9%. In addition, certain regions of Canada appear to exhibit an especially high prevalence of obesity, including most of the Atlantic provinces, northern Ontario, the Prairie provinces, Nunavut and the Northwest Territories (97,101). Overweight and obesity are now considered serious public health concerns in Canada, contributing to a dramatic increase in illnesses and accounting for nearly 57,000 deaths from 1985 to 2000. It has been estimated that in 2001, obesity-related disorders such as diabetes mellitus, hypertension, cardiac disease, stroke, blindness and some cancers resulted in $4.3 billion in direct and indirect costs to the Canadian health care system (104).

A November 2004 report issued by the Chief Medical Officer of Health in Ontario stated that obesity among children aged seven to 13 years tripled between 1981 and 1996. The incidence of type 2 diabetes has also tremendously escalated. Considering the long-term adverse consequences of childhood obesity, including type 2 diabetes and hypertension (formerly viewed as diseases of adulthood), comprehensive and multidisciplinary programs focusing on preventive measures are required to reduce the momentous obesity-related costs to the Canadian health care system. The Chief Medical Officer's report contains recommendations addressing all levels of government, school boards and the food industry, with the aim to put in place strategies for the intervention, treatment and prevention of childhood obesity (104). Obesity and the conditions associated with it (eg, type 2 diabetes, cardiac disease, stroke and blindness) are preventable or can be minimized by a proactive approach to wellness.

In brief, obesity is an important underlying risk factor for CVDs and other chronic diseases affecting millions of people worldwide in both developed and developing countries. Strategic international interventions should be put in place to prevent obesity from becoming the leading cause of premature preventable death due to diabetes, heart attack and stroke. In fact, unhealthy diet, obesity and diabetes are three of the nine significant risk factors identified by the INTERHEART study, as stated previously (12).

Effects of caloric restriction on obesity and longevity

It is important to consider the consequences of living in an era of 'super-sizing' and mass production. As a result of lower prices and abundant supplies of food, obesity has become a major health problem in North America. Obesity results from the North American trend toward unhealthy lifestyles, and action must be taken to impede the epidemic. With growing populations of obese people, public health promotion programs should consider the age-old practices of caloric restriction and fasting. Studies on flies, fish, mice and monkeys have shown that caloric restriction can have some striking benefits, such as delayed senescence, weight loss and increased lifespan. There appears to be a host of physiological factors through which these benefits are elicited, including neuroendocrine alterations (ie, suppression of gonadal, thyroid and growth hormones and insulin-like growth factor I, as well as activation of the adrenal glucocorticoid system), lower plasma leptin concentrations, decreased insulin concentrations, increased ghrelin concentrations, metabolic adaptation, altered endocrine function of adipose tissue and increased production of adipocytokines and proinflammatory cytokines (105,106). It may be worth mentioning that to maintain a healthy weight, caloric restriction should be coupled with physical activity and other healthy lifestyle practices.

Effects of obesity on drug disposition and therapeutic implications

The anatomical and physiological changes that occur with obesity may influence the absorption, distribution, metabolism and excretion of drugs. On the basis of the degree of lipophilicity, the volume of distribution and clearance of a drug may differ between obese and nonobese patients. Adipose tissue itself possesses a metabolic capacity that may be increased with excess fat mass. Given that many therapeutic agents are lipophilic and are typically widely distributed in adipose tissue, dosing regimens for obese patients may need to be adjusted for safety and effectiveness. Both glucuronidation and sulfate conjugation are increased in obese people and can affect the clearance or disposition of lorazepam and oxazepam. Single-dose studies have shown that the distribution volume and clearance of digoxin seem to be unaltered by obesity, whereas verapamil tends to have a lesser volume of distribution in obese patients. Administration of drugs in dosing regimens to obese patients based on results obtained in nonobese or lean people may increase the risk of toxicity or therapeutic failure. For drugs with a clearance that appears to be correlated with increasing weight, therapeutic dosing adjustments may be required for obese patients based on the pharmacokinetic and pharmacodynamic parameters of the medications. Boullata (107) has elegantly reviewed the influence of obesity on drug disposition and pharmacokinetic and pharmacodynamic effects.

INFLUENCE OF CIGARETTE SMOKING ON CVD

Ever since the United States Surgeon General's report in 1964 warned about the hazards of smoking, there has been some decline in the use of cigarettes. Despite these declines, tobacco smoking is still the leading preventable killer worldwide. Cigarette smoking can be held culpable for four million deaths annually throughout the world (108). It is estimated that by 2030, more than 10 million people will die annually of cigarette-related afflictions. It is estimated that in Canada alone, 45,000 people will die prematurely due to tobacco use, and at least 1000 people will die annually from secondhand smoke exposure (109). There are nearly 1.2 billion smokers worldwide (108,110), including approximately 45 million Americans (110) and five million Canadians (111). According to McCullough (112), approximately 62% of First Nation Canadians are smokers, whereas 31% of the remaining Canadians are smokers. Approximately 1.21 million Canadians aged 12 to 24 years are occasional or daily smokers (111). According to Ontario's Ministry of Health, smoking is the leading cause of preventable deaths, killing an estimated 16,000 people in the province every year. Tobacco-related diseases cost Ontario's health care system nearly $1.7 billion annually and result in $26 billion in productivity losses.

Within populations, smoking is especially prevalent among people with a lower socioeconomic status. These people buy cigarettes to fuel an addiction they cannot afford, thus perpetuating a vicious cycle. Tobacco companies are taking advantage of this addiction, and are promoting their products to low- and middle-income countries and populations, leading to soaring levels of cigarette use in those groups and geographical regions. Because of these reasons, the smoking rates in developing countries are steeply increasing, and cigarette smoking among Asian males is exorbitant: India (48%), Japan (53%), China (63%), Indonesia (69%) and Vietnam (73%) (108). In addition, tobacco companies have started to target their advertisement campaigns at a highly impressionable and susceptible group of people, namely, teenagers and adolescents.

Smoking during pregnancy causes intrauterine growth retardation, premature delivery and learning disabilities in the children whose mothers smoked during pregnancy. Because nicotine is excreted into breast milk, children of nursing mothers may become addicted to nicotine and may have nicotine withdrawal symptoms once weaned (113). Whalley et al (114) investigated the effect of smoking on childhood IQ and cognitive changes from 11 to 64 years of age. The results of this follow-up population-based Scottish Mental Survey showed an association between smoking, impaired lung function and rapid decline in cognitive performance at 64 years of age. The postulated mechanisms by which smoking may have adversely affected cognitive function in old age may be attributable to impaired lung function and cardiorespiratory support of brain function, as well as the direct deleterious effects of smoking on the lungs and brain. Smoking is also regarded as a risk factor for Alzheimer's disease (115).

By analyzing the data of 4411 respondents aged 15 to 54 years from the National Co-morbidity Survey, Lasser et al (116) observed that the likelihood of smoking is far greater in people with mental disorders (eg, depression, schizophrenia, bipolar illness or panic disorder) than those without. These findings emphasize the importance of focusing smoking prevention and cessation efforts on distinct populations, such as mentally ill patients.

There is overwhelming epidemiological and clinical evidence linking cigarette smoking with respiratory diseases (eg, cancer, chronic bronchitis, emphysema or asthma), development of thromboembolic complications, acute MI and stroke (108,110,117-123). The INTERHEART study investigators observed a clear dose-response relationship between smoking and the risk of acute MI. The harmful effects of smoking were seen even at relatively low levels, ie, those who smoked one to five cigarettes per day experienced a 40% increase in MI risk compared with nonsmokers, whereas those who smoked six to 10 cigarettes per day had a twofold increase in risk, and those who smoked 20 cigarettes per day had a fourfold increase in risk of heart disease. This large international case-controlled study also found that irrespecitve of the device used for tobacco smoking (ie, filtered or nonfiltered cigarettes, bidis [a popular South Asian cigarette], pipes or cigars), all had similar risks for MI (11); therefore, it appears that any amount and any form of tobacco smoking is injurious to health.

Cigarette smoking increases the risk of hypertension, CAD, stroke and peripheral vascular disease. Smoking-induced endothelial dysfunction and inflammation promote atherosclerotic plaque and thrombus formation. In addition, smoking seems to enhance the multiplicative effects of other risk factors associated with CAD. According to Burns (123), smoking per se increases the risk of developing CAD twofold. However, when combined with other risk factors such as elevated serum lipid concentrations, uncontrolled hypertension and diabetes, the risk of CAD is compounded exponentially, to the extent that a combination of any three risk factors would correspondingly increase the development of CAD eightfold.

Besides other health problems, smokers are at a greater risk of developing erectile dysfunction or male impotency. Smoking cessation improves not only erectile function, but also response to pharmacotherapy (eg, sildenafil, tedalafil

and vardenafil) of erectile dysfunction. Chronic smoking has been shown to decrease the activity of endothelial nitric oxide synthase and impair the release of nitric oxide in penile tissue. Nitric oxide activates the enzyme guanylyl cyclase, which results in increased concentrations of cyclic GMP. The increased concentrations of cyclic GMP cause smooth muscle relaxation in the corpus cavernosum and allow for an increased flow of blood into the penis, resulting in erection (124).

The three main biologically active ingredients in cigarette smoke that have been touted as causal constituents for heart disease and stroke are nicotine, carbon monoxide and oxidant gases. Nicotine causes stimulation of autonomic ganglia and the central nervous system. By increasing the activity of the sympathetic nervous system, nicotine increases the release of catecholamines, which in turn elevates heart rate and BP, resulting in wear and tear on the arterial walls. Nicotine affects other systems as well, including the release of other endogenous opioids and glucocorticoids. Nicotine is readily absorbed through the skin, mucous membrane and lungs. Because of its rapid absorption from the pulmonary route, inhalation of cigarette smoke delivers approximately 15 ng/mL blood of nicotine within the first 10 min, whereas other sources and routes of administration, such as chewing tobacco, nicotine gum, nasal snuff and nicotine patches, take at least 30 min to release the same amount of nicotine into the bloodstream. The average plasma half-life of nicotine in smokers is 40 min. The biotransformation of nicotine takes place in the liver, where CYP2A6 converts it to its major metabolite cotinine, which is further metabolized by oxidation to hydroxycotinine and a ring cleavage product. Only approximately 5% of nicotine is excreted unchanged in the urine along with its metabolites. Nicotine is a highly addictive and dependence-producing substance, as is exemplified by the high failure rate among smokers who try to quit (125).

Carbon monoxide has a high affinity for hemoglobin and competes with oxygen for uptake by red blood cells. The production of carboxyhemoglobin leads to reduced oxygen supply to the tissues, thereby producing hypoxemia. To compensate for lowered oxygen uptake, more red blood cells are generated, leading to polycythemia and increased blood viscosity, and consequently increasing the risk of thrombus formation.

Smoking-induced hypoxemia elevates the degree of oxidative stress in the body. Oxidative stress is thought to generate free radicals that contribute to endothelial inflammation and dysfunction, plasma lipid abnormalities through oxidation of LDL, and platelet adhesion activation. Lipid peroxidation also plays a vital role in atherogenesis because it leads to the development of foam cells (the initial components of endothelial plaques). All of these combined actions of cigarette smoking play an important role in the initiation and development of CVD. A diagram of the pathophysiological actions of cigarette smoking and acute coronary events is shown in Figure 7 (122).

Although various clinical and epidemiological studies have shown the harmful effects of chronic smoking on cardiovascular health (117,119), other studies have reported that quitting smoking not only improves cardiovascular health, but also enhances longevity (110,117,118,120,121). It has been shown that smoking cessation improves overall health and reduces the risk of heart disease and stroke; however, risk remains elevated for approximately a decade after discontinuation (123). For example, Wiggers et al (121) reported that after one year of smoking cessation, the risk of CAD may be reduced by greater

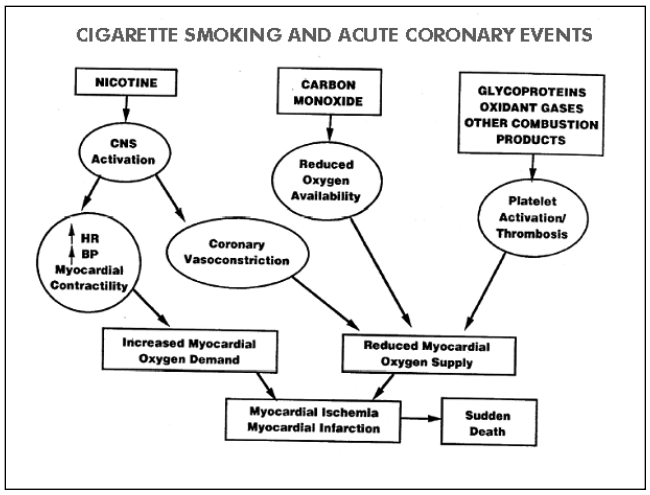

Figure 7) *Diagram of the pathophysiological effects of cigarette smoking. The main biologically active ingredients in cigarette smoke are nicotine, carbon monoxide and various other oxidant gases. ↑ Increased; BP Blood pressure; CNS Central nervous system; HR Heart rate. Reproduced with permission from reference 122*

than 50%, and within several years of discontinuation, risk returns to that of life-long abstainers. This type of evidence clearly suggests that sustained health benefits may be achieved by quitting smoking and by introducing health promotion and preventive measures for smoking cessation.

Considering the mortality and morbidity rates, as well as hospitalization costs, the health protection and promotion authorities of all countries should design intervention frameworks to deal with long-term smoking-associated problems. At the same time, both the regulators and citizens should challenge the marketing of hazardous products by the tobacco companies.

A few years ago, the Canadian Federal Government introduced legislation that banned cigarette smoking inside government buildings. Currently, legislation is being enacted by the Government of Ontario to outlaw smoking in all public and work places by May 2006. The antismoking legislation is also expected to cover retail displays of cigarettes, banning the power-wall cigarette displays found in various variety stores and gas stations. Some municipalities have enacted bylaws to ban smoking in bus shelters, buses, trains, restaurants, bars and municipal buildings. Despite these laudable legislative measures, cigarette smoking remains a major health concern in adults and teenagers in Canada.

Because cigarette smoking is the leading preventable cause of death and cardiorespiratory diseases, global public health interventions for stopping smoking should focus on all populations. Special attention, however, should be paid to selected groups, such as pregnant and nursing mothers, teenagers and adolescents, persons with mental illness and those with a lower socioeconomic status.

Effects of smoking on drug disposition and therapeutic implications

Cigarette smoke is a complex mixture of volatile and particulate matter. Some 500 gaseous compounds, including nitrogen, carbon monoxide, carbon dioxide, ammonia, hydrogen, cyanide and benzene, have been identified in the volatile phase, whereas approximately 3500 different compounds have been

detected in the particulate material, of which, the major compound is the alkaloid nicotine. The polycyclic aromatic hydrocarbons present in tobacco smoke are thought to be responsible for the induction of cytochrome P450 (CYP) isozymes, namely, CYP1A1, CYP1A2 and CYP2E1. CYP1A1 is primarily an extrahepatic enzyme found in the lungs and placenta, whereas CYP1A2 and CYP2E1 have been identified in the liver, lung, small intestine, brain and kidneys. Some isoforms of uridine 5′-diphosphate glucuronosyltransferase that are involved in phase II glucuronidation reactions are also induced by chronic smoking. In mice, cigarette smoke causes the induction of CYP2E1 in the liver, lungs and kidneys, and nicotine accelerates the metabolism of CYP2E1 substrates in liver microsomes of the rat (126). Animal studies (126) also indicate that nicotine may have an inducing effect on CYP2B1 and CYP2B2, and may also modify the activity of CYP2A1 and CYP2A2. Carbon monoxide tends to have inhibitory effects on some hepatic CYP isozymes and, in rats, it has been shown to inhibit the metabolism of some drugs. Heavy metals such as cadmium, present in cigarette smoke, may decrease the activity of CYP2E1 (126).

Cigarette smoking can significantly enhance the activity of CYP2E1 in humans and, consequently, can accelerate the metabolism and disposition of psychoactive drugs (eg, imipramine, haloparidol, pentazozine and oxazepam) and cardiovascular drugs (eg, propenalol, theophylline and heparin). CYP2E1 metabolizes a number of compounds, including acetaminophen and ethanol, as well as activating many carcinogens, including nitrosamines. Induction of CYP2E1 activity by cigarette smoking is indicated in tobacco-induced cancer, alcohol-induced liver disease and increased risk of acetaminophen hepatotoxicity (126).

Cigarette smoking is associated with a faster clearance of heparin, possibly due to an increased binding of heparin to antithrombin III, which thereby increases the prothrombotic effects of cigarette smoking. Owing to the shorter half-life of heparin in cigarette smokers, these patients may require larger doses of heparin to achieve an anticoagulant effect equivalent to that in nonsmokers. The anticoagulant action of warfarin is not significantly affected during smoking. However, evidence indicates that β-blockers and antiarrythmics are rendered less effective because of their faster metabolism and renal clearance in smokers (126,127).

In humans, phenotypic differences have been reported in the inducibility of drug metabolizing enzymes, suggesting that the effects of smoking on drug metabolic pathways are not absolutely predictable (127). The impact of cigarette smoking on drug metabolism and disposition should be carefully assessed not only when prescribing drugs to smokers, but also when selecting patients for clinical trials, because pharmacokinetic and pharmacodynamic results obtained in smokers may not be applicable to the nonsmoking population.

CONCLUSIONS

Evidence gathered in the present review indicates that regular moderate physical activity (approximately 30 min/day) has highly beneficial effects in lowering BP, decreasing blood coagulation, improving fibrinolytic capacity and helping in vascular remodelling. In addition, exercise assists in improving plasma lipid profiles by increasing the HDL-C to total cholesterol ratio and reducing the LDL-C to total cholesterol ratio. Dietary modifications involving a decreased intake of saturated and trans fats and increased ingestion of fresh fruits and vegetables have also proved useful in limiting the progression of CVDs and some chronic diseases. Definitive evidence was provided by the findings of the case-controlled INTERHEART study, which showed that approximately 80% of CVD-related mortality and morbidity is preventable by exercise, healthy dietary habits, maintaining a healthy body weight and by not smoking (11).

Mediterranean-type diets, as well as foods high in fibre and low in glycemic load, are associated with a decreased prevalence of metabolic syndrome and diabetes mellitus and improved serum lipid concentrations.

Overweight and obesity are serious public health challenges that affect millions of people in developed and developing countries. Obesity is a major modifiable risk factor that contributes heavily to the onset of diabetes mellitus, hypertension, heart disease, stroke and some cancers. Healthy dietary habits and lifestyle changes such as physical activity and moderate alcohol consumption have been positively linked with a reduction in obesity.

Finally, countless studies have documented that smoking contributes heavily to the development of CVD and respiratory diseases. It has consistently been shown that smoking increases the risk of atherosclerosis and interferes with the normal functioning of the cardiopulmonary system. Because tobacco smoking is an avoidable risk factor for CVD and respiratory diseases, interventions to stop smoking should be highly encouraged in all age groups, especially in younger populations.

Given the scope and prevalence of CVDs, a population health approach – 'prevention is better than cure' – would be the most appropriate model to adopt to deal with CVD-related mortality and morbidity. Prophylactic measures must be dealt with collectively because an ample amount of scientific evidence indicates that lifestyle modifications, including nutritional interventions, increased physical activity, decreased incidence of obesity and smoking cessation, would provide an integrative approach for the prevention of heart disease and stroke. Such preventive approaches would help in reducing not only employee absenteeism, but also the hospital, drug and physician service costs burdening the private and publicly funded health care systems.

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