Cardiovascular disease and osteoporosis: Balancing risk management

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Abstract: In this narrative review of the current literature, we examine the traditional risk factors and patient profiles leading to cardiovascular disease and osteoporosis. We discuss the interrelationships between risk factors and common pathophysiological mechanisms for cardiovascular disease and osteoporosis. We evaluate the increasing evidence that supports an association between these disabling conditions. We reveal that vascular health appears to have a strong effect on skeletal health, and vice versa. We highlight the importance of addressing the risk benefit of preventative interventions in both conditions. We discuss how both sexes are affected by these chronic conditions and the importance of considering the unique risk of the individual. We show that habitual physical activity is an effective primary and secondary preventative strategy for both cardiovascular disease and osteoporosis. We highlight how a holistic approach to the prevention and treatment of these chronic conditions is likely warranted.

Keywords: osteoporosis, cardiovascular disease, risk management

Introduction

Cardiovascular disease (CVD) and osteoporosis (ie, reduced bone mass and microarchitectural deterioration of bone) are major health problems in North America, whose incidence increases with advancing age (Warburton et al 2006a). The socioeconomic and health care burden of osteoporosis and CVD on society is enormous (Johnell 1997). Osteoporotic fractures (Braithwaite et al 2003) and CVD-related events are key origins of morbidity and premature mortality in the elderly (Warburton et al 2006a). Moreover, post-menopausal women appear to be particularly at risk for developing both osteoporosis and CVD. In fact, once a woman reaches menopause, the risk for both osteoporosis and CVD increases substantially. Moreover, CVD and osteoporosis are often observed in the same individual (Schulz et al 2004).

Globally, CVD is a major cause of premature mortality accounting for approximately one-third of the cases of death. According to the World Health Organization approximately 17 million people die as a result of CVD each year (World Health Organization 2006).

In the United States, approximately 10 million individuals have osteoporosis and approximately 34 million are at an increased risk owing to low bone mass (National Osteoporosis Foundation 2007). Approximately 80% of those affected with osteoporosis are women (National Osteoporosis Foundation 2007). In Canada, approximately 1.4 million suffer from osteoporosis (Osteoporosis Canada 2007). In North America, 20%–25% of women over the age of 50 have osteoporosis (Osteoporosis Canada 2007) and approximately 50% are estimated to have low bone mass (National Osteoporosis Foundation 2007).

For years, osteoporosis and CVD were thought to be independent chronic diseases that increased markedly with advancing age. However, increasing evidence now supports a direct association between these chronic conditions. Accordingly, in this

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article we review the risk factors and patient profiles leading to both CVD and osteoporosis. Moreover, we review the mounting evidence that reveals an association between these diseases. We also discuss methods of reducing the risk for each chronic condition and the effects of these interventions on the subsequent risk for each disease. We discuss the differential rates with which osteoporosis and CVD affect men and women, and highlight how a holistic approach to these chronic conditions is warranted.

Traditional risk factors and patient profiles

Cardiovascular disease

Several traditional major independent risk factors for CVD have been identified including non-modifiable (family history, male sex, and advancing age) and modifiable risk factors. The major modifiable risk factors for CVD include elevated blood pressure, cigarette or tobacco smoking, physical inactivity, abnormal lipid lipoprotein profiles (eg, high total cholesterol, LDL cholesterol and triglycerides levels, and low levels of HDL cholesterol), unhealthy diets, excessive alcohol use, obesity, and diabetes.

Recent research has also identified several "emerging" or "novel" risk factors that are independent predictors of CVD and premature mortality. This includes factors such as vascular health (eg, arterial compliance, carotid intima media thickness, and pulse wave velocity), left ventricular mass, and a series of novel blood parameters (eg, lipoprotein (a), fibrinogen, C-reactive protein, and homocysteine). The measurement of "emerging" risk factors in combination with a traditional lipid panel is thought to provide "information on risk over and above that supplied by established risk factors" (Heinrich and Assmann 1995).

The majority of CVD events are the result of atherosclerosis (Grey et al 2003). The endothelium plays an important role in the process of atherosclerosis and thus has a significant effect on the long-term risk for CVD (Leeson et al 1997). Endothelial dysfunction is thought to be an obligatory first step in the process of atherosclerosis and has been observed in patients with coronary atherosclerosis (Sorensen et al 1997) and individuals with risk factors for CVD (Celermajer et al 1994). Therefore, a healthy endothelium is essential for the protection against atherosclerosis (Anderson 2003). Endothelial dysfunction has been associated with multiple CVD risk factors and has also been reported to occur prior to the development of atherosclerosis (Celermajer et al 1992; Whitney et al 2004). It is important to note, that endothelial dysfunction has been observed in multiple chronic disease states including coronary artery disease, stroke, chronic heart failure, type 2 diabetes, hypertension, and obesity (Warburton et al 2006a).

Cardiovascular disease places a significant burden upon health care systems worldwide. In Canada, CVD (including heart disease and stroke) is the leading cause of death (accounting for over one-third of all deaths) disability, and hospitalization accounting for approximately 17% of the total health care costs (Wilson and Wielgosz 1999; Health Canada 1999; Katzmarzyk et al 2000). Cardiovascular diseases cost the Canadian economy $18 billion a year (Public Health Agency of Canada 2002). Fortunately, CVD is largely preventable.

In developed countries, many adults have one or more risk factor for CVD. For instance, 80% of Canadians have one or more risk factor for CVD (Health Canada 2005). As illustrated in Figure 1, the prevalence of modifiable risk factors for CVD in developed countries is alarming. Perhaps of more concern is the finding that many children and adolescents have risk factors for CVD. For instance, in a recent study we revealed that 58% of children (10–11 yr) had at least one elevated CVD risk factor and approximately 8% of the children had four or more elevated CVD risk factors (McKay et al 2004). Clearly, effective prevention and treatment interventions are required across the lifespan.

Osteoporosis

Several non-modifiable and modifiable risk factors have been identified for osteoporosis. Non-modifiable risk factors include female sex (women are at greater risk), advancing age, personal history of a fracture after age 40, family history of osteoporosis, European or Asian ancestry, and dementia. Potentially modifiable factors include low BMI, calcium and vitamin D intake deficiency, physical inactivity, certain medications (eg, excessive use of corticosteroids), estrogen deficiency, current cigarette smoking, excessive alcohol consumption, early menopause (before age 45), and prolonged pre-menopausal amenorrhea (>1 year) (Brown and Josse 2002; Canadian Multicentre Osteoporosis Study 2006).

Osteoporosis is a major health burden affecting millions of people worldwide (particularly in developed countries) (World Health Organization 2003). In Canada approximately one in four women and one in eight men (over the age of 50) will have osteoporosis (Hanley and Josse 1996; Brown and Josse 2002). In developed countries, it has been estimated that 40%–54% of 50 yr old women will have an osteoporosis-related fracture during their lifetime (Chrischilles et al 1991; Melton et al 1992). The prevalence is higher amongst

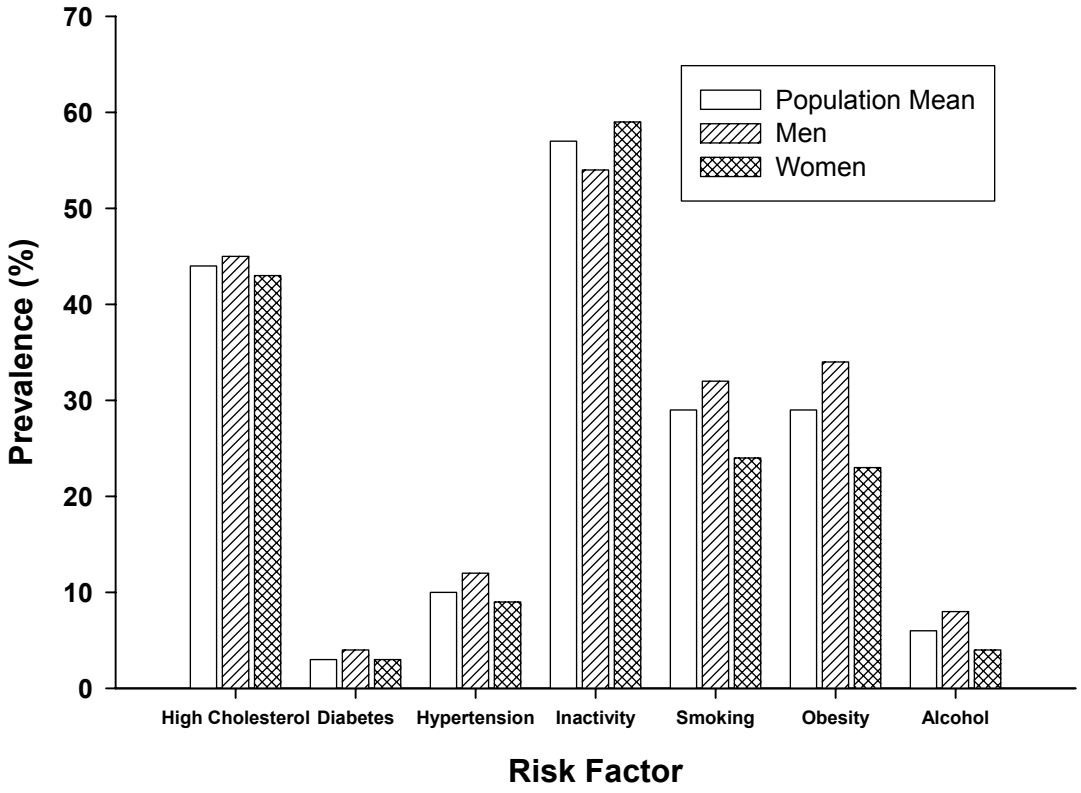

Figure 1 Prevalence of traditional risk factors for cardiovascular disease in Canadian society according to gender.
Note: High cholesterol was defined as a plasma cholesterol level above of 5.2 mmol·L^{-1}; Diabetes was evaluated by self-report; Hypertension was defined as a blood pressure of ≥140/90 mmHg; Inactivity was defined as an usual daily leisure-time energy expenditure of <1.5 kcal·kg^{-1}·day^{-1}; Smoking was defined as daily tobacco smoking; Obesity was defined as a body mass index of >27; Alcohol was defined as alcohol use in excess of 9 and 14 drinks per week for women and men, respectively.
Source: Statistics Canada, National Population Health Survey, 1996/97 and the Heart and Stroke Foundation of Canada, The Changing Face of Heart Disease and Stroke in Canada 2000, October 1999 (Heart and Stroke Foundation of Canada 2000, Statistics Canada 1999b).

older adults; however, osteoporosis can present itself at any age (Canadian Multicentre Osteoporosis Study 2006). The incidence of osteoporosis is positioned to increase markedly over the next few decades owing to the increasing numbers of older individuals worldwide (Brown and Josse 2002; Canadian Multicentre Osteoporosis Study 2006).

The burden osteoporosis places upon the individual, the family, and society as a whole is enormous. In Canada (1996 data) hip fractures were the second leading cause of hospital admission for women aged 65 years or older (Statistics Canada 1999a). It has been estimated that without the creation of effective prevention and treatment strategies Canada will spend $1.9 billion per year to treat osteoporosis and related fractures (Osteoporosis Canada 2007).

Health-related quality of life is often markedly reduced in persons with osteoporosis. It has been estimated that 50% of women who sustain a hip fracture will become functionally dependent during activities of daily living, and 20% will require long term care (Chrischilles et al 1991; Brown and Josse 2002). Moreover, the incidence of premature mortality is 20% higher within a year of suffering a hip fracture (Chrischilles et al 1991; Brown and Josse 2002). Fortunately, osteoporotic fractures are preventable (Brown and Josse 2002).

The interrelationships between risk factors for cardiovascular disease and osteoporosis

In recent years, a growing body of literature (see Table 1) has revealed an association between CVD and osteoporosis. In particular, epidemiological evidence has shown a relationship between vascular calcification and bone loss (as reviewed in Table 1). For instance, bone mineral density has been inversely associated with coronary and/or aortic calcification (Uyama et al 1997; Barengolts et al 1998; Bagger et al 2006), and directly associated with high-density lipoprotein cholesterol (HDL-C) (Yamaguchi et al 2002) (Table 1).

Clinical populations have also revealed a relationship between CVD and osteoporosis. For instance, accelerated bone

Table 1 Relationship between vascular and bone health

Investigation	Design	Population	Primary outcome measures	Key results
(Browner et al 1991)	Prospective, 2.8y	9074 women, >65y	BMD (SPA); cause of death (ICD-9 codes)	• Each SD decrease in BMD of proximal radius resulted in a 70% increase stroke mortality. • Age-adjusted BMD revealed a weak association with CV mortality.
(Uyama et al 1997)	Observational	30 women, 67–85y	BMD (DXA); carotid plaque score (ulltrasound)	• Linear correlation with BMD and plaque score. • No association with L2-L4 BMD and plaque.
(Vogt et al 1997a)	Observational	1292 women, mean age 71y	Blood flow-ankle/arm index; posterior tibial and brachial systolic BP; BMD (SPA and DXA)	• >1SD change above mean annual index change resulted in reduced BMD at hip 2 fold vs. smallest SD change. • A decrease of 2 SD in ankle/arm index was associated with a 3.7% decrease in hip BMD.
(Vogt et al 1997b)	Observational	2051 women, >65y	Aortic calcification (lateral radiographs); BMD (DXA)	• No significant association.
(Barengolts et al 1998)	Observational	11 controls, 20 osteopenic, 14 women with osteoporosis, mean age 65y	BMD (DXA), coronary calcium (QCT)	• Osteoporosis group had a significantly higher calcium score vs controls.
(von der Recke et al 1999)	Longitudinal observational	309 women, mean age 50y	Bone mass/BMC (SPA of forearm and lateral radiography of spine)	• 50y group: Each SD decrease in bone mass resulted in a 43% increase in all cause mortality and 2-fold increase in CV death.
	Recruited 1977–88, assessed 1994	754 women, mean age 70y	Cause of death (ICD-9 codes)	• 70y group: Bone mass in lowest quartile was associated with a 2 fold increased risk of CV death vs highest quartile.
(Hak et al 2000)	Longitudinal observational for >9y	236 women, 45–64y	Aortic calcification (radiographs), MCoA and RCoA	• Progression of aortic calcification was associated with decreased MCoA (6.1%) and RCoA (8.9%).
	Cross-sectional	720 women, mean age 63y		• No progression was associated with decreased MCoA (3.9%) and RCoA (6.9%). • Inverse, graded, association between extent of aortic calcification and MCoA/RCoA.
(Kado et al 2000)	Longitudinal observational, 5.7y	6046 women, mean age 76y	Rate of BMD loss; cause-specific mortality	• Each SD increase in rate of bone loss resulted in 1.3-fold increase in the risk of CHD death, 1.2-fold increase in the risk of atherosclerotic death and 1.6-fold increase in the risk of death due to pulmonary causes.
(Kiel et al 2001)	Longitudinal observational, 25–30y	346 women, 190 men, 28–62y at start of study	Cortical bone mass (radiogrammetry); aortic calcification (radiographs)	• Each percent decrease of MCoA was associated with 7.3% increase in aortic calcification index in women.
(Aoyagi et al 2001)	Observational of a prospective cohort	524 Japanese American women, 43–80y	BMD of distal/proximal radius and calcaneus (SPA); aortic calcification (lateral and AP radiographs)	• No significant association between osteoporosis and aortic calcification.
(Yamaguchi et al 2002)	Observational	214 women, 47–86y	BMD, TC, LDL-C, HDL-C, TG	• Inverse correlation with BMD and LDL-C. • Positive correlation with BMD and HDL-C.

(*Continued*)

Table (continued)

Investigation	Design	Population	Primary outcome measures	Key results
				• Low TG levels associated with vertebral fracture.
(Tanko et al 2003)	Observational	963 women, 60–85 yr	Aortic calcification (graded on lateral lumbar radiographs), and BMD (at the distal radius, lumbar spine, proximal femur)	• Age, years since menopause, BMI, level of education, smoking history, and physical activity were significant common risk factors for AC and hip BMD. • Aortic calcification was an independent predictor of hip BMD. • In a subgroup analysis, women with a history of intermittent claudication showed more severe aortic calcification, lower hip BMD, and a higher prevalence of CHD compared to age-matched controls.
(Kiechl et al 2004)	Prospective, longitudinal (10 yr) population-based survey	N = 915, approximately 50% males and females (Mean Age approximately 59 yr)	Serum OPG, incident CVD, carotid atherosclerosis	• Prevalence and severity of carotid atherosclerosis increased progressively with higher levels of OPG (even after controlling for sex and age). • OPG was a significant and independent risk factor for 10-year incident cardiovascular disease and vascular mortality.
(Schulz et al 2004)	Observational Cross-sectional and Longitudinal	*Cross-sectional*: 2348 postmenopausal women (50yrs and older) *Longitudinal:* 228 postmenopausal followed 9 months to 8 yr later	Aortic calcification, BMD, fracture	• *Cross-sectional:* Age-independent association between the degree of aortic calcification and bone density. • Aortic calcification was associated with a 4.8 and 2.9-fold increase in the risk for vertebral and hip fractures, respectively. • Bilateral hip fractures more common in those with calcification than those without. • *Longitudinal:* Graded relationship between bone loss and the progression of vascular calcification.
(Magnus and Broussard 2005)	Observational	5,050 women and men aged 50–79 yr	BMD, MI (self-report), BMI, glucose, cholesterol, HDL, medications (self-report)	• Participants who reported prior MI had significantly higher odds of having low BMD (after adjusting for CVD and osteoporosis risk factors). • MI was significantly associated with low BMD in men, but not women.
(Tanko et al 2005)	Multicenter, randomized, double-blinded, placebo controlled Followed for 4yrs	2576 women, mean age = 66.5 yr (assigned to placebo group)	Incidence of fatal or nonfatal CV events, BMD (femoral neck and lumbar spine), traditional risk factors for CVD (BMI, blood pressure, smoking habit, lipid profile, and history or presence of hypertension, diabetes, hyperlipidemia, cardiovascular disease, and/or related major interventions)	• Osteoporotic women had a 3.9-fold increased risk for cardiovascular events than women with low bone mass. • Risk of cardiovascular events increased incrementally with the number and increasing severity of baseline vertebral fractures. • Composite cardiovascular risk was higher in women with osteoporosis and they were also more frequent users of cardiovascular medications. • The incidence of an acute cardiovascular event during the follow up was higher in women with osteoporosis (evident for both coronary and stroke events).

(*Continued*)

Table (continued)

Investigation	Design	Population	Primary outcome measures	Key results
				• Increased risk for cardiovascular events associated with osteoporosis could not be explained by common risk factors alone.
(Bagger et al 2006)	Longitudinal observational, 7.5 yr	N = 2662 Postmenopausal women, mean age = 65 yr	Aortic calcification, BMD, vertebral fractures (X-ray), hip fractures (self-report)	• Advanced aortic calcification at baseline was significantly related to lower BMD and accelerated bone loss at the proximal femur. • The severity of aortic calcification was an independent predictor of hip fractures (OR = 2.3).
(Hermann-Arnhof et al 2006)	Observational	97 patients undergoing elective coronary artery bypass surgery	OPG, cardiac troponin I, electrocardiography, homocysteine, C-reactive protein	• Positive correlation between OPG before surgery and the number of diseased vessels. • Positive correlation between OPG before surgery and the number of bypasses. • Strong correlation between OPG before surgery and homocysteine • OPG level for four patients who experienced cardiac complications was elevated.
(Sinnott et al 2006)	Observational	313 women (57 yr) and 167 men (55 yr)	Coronary calcium burden, BMD, self-report CHD risk factors, medical history	• The degree of coronary calcification was inversely associated with BMD in postmenopausal women. After controlling for age, this association was absent.
(Jorgensen et al 2006)	Prospective, longitudinal, 6 yr	2,733 women, aged 55-74 yr	Carotid Artery (echogenic) plaques, nonvertebral fractures	• The age-adjusted relative risk of fracture was significantly higher in women with echogenic plagues (1.7 (95% confidence interval 1.0–2.7).
(Bagger et al 2007)	Observational	176 women, aged 60–85 yr	Genotyped for epsilon (varepsilon) allelic variants of the ApoE gene, and measures of serum lipids (total cholesterol, triglycerides, HDL-C, LDL-C, apoA1, ApoB, Lp(a)), hip and spine BMD, aorta calcification, radiographic vertebral fracture and self-reported wrist and hip fractures, and cardiovascular events	• Presence of the ApoE varepsilon4 allele was associated with a worsened serum lipid profile, but had no association with spine/hip BMD or aortic calcification. • After adjusting for age, the risk of hip fractures but not wrist or vertebral fractures was increased in subjects with advanced vascular disease.

Abbreviations: AP, anterior posterior; BMC, bone mineral content; BMD, bone mineral density; BP, blood pressure; CHD, coronary heart disease; CV, cardiovascular; DXA, dual energy x-ray absorptiometry; HDL-C, high-density lipoprotein-cholesterol; ICD-9, International Classification of Diseases (9th edition); L_{2-4}, 2nd through 4th lumbar vertebrae; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; MCoA, metacarpal cortical area; PM, postmenopausal; QCT, quantitative computed tomography; RCoA, relative cortical area; SD, standard deviation; SPA, single photon absorptiometry; TC, total cholesterol; TG, triglycerides; OR, odds ratio; IMT, intimal medial thickening; OPG, osteoprotegerin; BMI, body mass index; MI, myocardial infarction.

loss has been observed in diabetics (Schwartz et al 2005), a group that commonly exhibits marked vascular dysfunction (Romney and Lewanczuk 2001; McGavock et al 2004). Furthermore, in cases where vascular function is affected differentially on opposite sides of the body (ie, asymmetric vascular disease in the lower limbs), the side that has the greatest vascular dysfunction also displays the lowest bone mineral content (Laroche et al 1994; Laroche et al 2003). Moreover, in elderly individuals who have experienced a fracture at the femoral neck, the blood vessels supplying the proximal femur are often atherosclerotic (Bocchi

et al 1985; Bocchi et al 1987). The rate of bone loss at the hip has also been shown to be greater in women who have the greatest reductions in blood flow (as assessed by the ankle/arm index) (Vogt et al 1997a).

The potential relationship between these chronic conditions has important implications for the health of many individuals with (or at risk for) CVD and osteoporosis (Table 1) (Tanko et al 2005). For instance, investigations with post-menopausal women have observed that there is an increased risk of cardiovascular-related and stroke mortality for each standard deviation decrease in bone mass (Browner et al 1991; von der Recke et al 1999; Kado et al 2000). For instance, Kado et al (2000) revealed that for each standard deviation decrease in bone mass there was a 1.2- to 1.3-fold increased risk of dying from coronary artery disease or other forms of atherosclerosis. von der Recke et al (1999) reported that the lowest quartile of bone mass was associated with a 2-fold increase in the risk for CVD-related death (vs. the highest quartile). Tanko et al (2005) revealed that osteoporotic women had a 3.9-fold increased risk for cardiovascular events than women with low bone mass. This increased risk could not be explained by common risk factors alone. It is important to note however that studies have also shown no relationship between coronary calcification and osteoporosis after controlling for age (Sinnott et al 2006).

It remains to be determined the key mechanism(s) responsible for the relationship between CVD and osteoporosis. As identified above, both chronic conditions share similar modifiable risk factors (such as physical inactivity, smoking, age, years since menopause, and excessive alcohol usage). However, researchers have shown a direct relationship between vascular disease and hip bone mineral density even after adjusting for a wide range of common risk factors (including age, years since menopause, BMI, level of education, current and previous smoking, and physical inactivity) (Tanko et al 2003). Therefore, CVD and osteoporosis also may be linked by common pathophysiological mechanisms (Tanko et al 2003). The available epidemiological evidence does not allow for the establishment of a causal link between CVD and osteoporosis. However, there are plausible biological pathways whereby diminished cardiovascular health can influence bone health and vice versa (Whitney et al 2004). Several excellent reviews have been created recently on these topics (Doherty et al 2003; Hamerman 2005; Rajzbaum and Bezie 2006).

Potential mechanisms

There is evidence that vascular calcification has several common features to bone formation at both the cellular and molecular level. As stated by Doherty et al (2003) "calcified atherosclerotic arteries can contain tissue that is histomorphologically indistinguishable from bone." Vascular calcium deposition is now thought to be an active, complex, and regulated process similar to new bone formation (or remodeling) that is not merely a consequence of aging (Doherty et al 2003; Rubin and Silverberg 2004). Importantly, calcifying vascular cells appear to have the ability to experience osteoblast differentiation (Rubin and Silverberg 2004). Moreover, it has been hypothesized that there are arterial cells that can differentiate into mineral resorbing cells (ie, osteoclast-like cells) (Doherty et al 2002). These cells are thought to be derived from hematopoietic precursors of the mononuclear phagocytic lineage (Doherty et al 2002). Doherty et al (2002) postulated that osteoclast-like cells may play a role in the delicate balance of mineral deposition and resorption within the arterial wall (similar to that seen in bone). These authors also considered arterial mineral deposition "as a localized failure of protective mechanisms that actively oppose mineral deposition within the disordered metabolic milieu of developing atherosclerotic plaque." This supports a growing body of research that indicates that arterial calcification involves arterial osteoblast- and osteoclast-like cells (Doherty et al 2003).

Both the artery wall and the osteon of cortical bone have a common endothelium lined lumen. Cancellous bone is also highly vascular. Moreover, calcified plaque has been shown to have numerous cellular and molecular elements that participate in bone formation including (but not exclusive to) bone morphogenetic protein-2, collagen 1, osteonectin, osteopontin, matrix Gla proteins, osteocalcin and osteoprotegerin (Doherty et al 2003; Whitney et al 2004; Hamerman 2005).

Several biological mechanisms (based primarily on animal models) have been proposed to explain the link between CVD and osteoporosis (see reviews of Doherty et al 2003; Hamerman 2005; and Rajzbaum and Bezie 2006). Chronic inflammation is known to play a role in the development of both chronic conditions. For instance, proinflammatory cytokines (including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α)) have been associated with vascular disease (Blake and Ridker 2001) as well as increasing bone resorption (Cohen-Solal et al 1993). Also, both bone and the vasculature are affected by sex steroids (Stevenson 2004; Rossouw 2005). For example, estrogens play a role in CVD and osteoporosis via their effects on cytokines (including IL-6, osteoprotegerin (as discussed later), and TNF-α) (Baldini et al 2005).

As outlined above, vascular calcifications and bone have several similarities (Hamerman 2005; Rajzbaum and

Bezie 2006). Several compounds found within arterial wall calcifications have been implicated in the association between bone loss and CVD. For instance, osteoprotegerin (an important regulator of osteoclastgenesis) has recently received considerable attention. Osteoprotegerin is a member of the TNF receptor superfamily that serves as a bone resorption inhibitor by blocking the RANK-L/RANK interaction (Kiechl et al 2004; Rajzbaum and Bezie 2006). Animal and human studies have reported conflicting findings regarding the role of osteoprotegerin in CVD and osteoporosis. Mice that do not have the osteoprotegerin gene exhibit vascular calcifications and osteoporosis (Bucay et al 1998). The intravenous administration of osteoprotegerin into mice deficient in osteoprotegerin reversed the osteoporosis, but it did not correct the arterial calcification. Whereas, the transgenic osteoprotegerin gene delivered during gestation prevented the formation of arterial calcification in osteoprotegerin deficient mice (Min et al 2000). In humans, a high level of osteoprotegerin has paradoxically been shown to be an independent risk factor for the progression of atherosclerosis and the development of CVD (Browner et al 2001; Kiechl et al 2004). Similarly, high levels of osteoprotegerin were observed in post-menopausal women with osteoporosis (Yano et al 1999). Based on animal literature, it would be anticipated that high osteoprotegerin levels would be associated with high bone mineral density (Hamerman 2005). Yano et al (1999) postulated that the high osteoprotegerin levels (in osteoporotic post-menopausal women) may reflect a compensatory response to enhanced osteoclastic bone resorption.

Serum lipids (a well-established risk factor for atherogenesis) have been proposed as one common mechanism for CVD and osteoporosis. It has been postulated that oxidized lipid accumulation in the subendothelial space of arteries promotes arterial calcification and inhibits bone mineral formation (Parhami et al 2000). Lipids have been shown to have effects on osteoblasts (Parhami et al 1997, 2000, 2002) and osteoclasts (Tintut et al 2004). For instance, the same oxidized lipids that bring about osteoblast differentiation in calcifying vascular cells inhibit osteoblast differentiation in bone cells of mice (Parhami et al 1997). Moreover, in atherogenic susceptible and resistant mice exposed to a high fat or normal diet, a 35% decrease in both bone mineral content (BMC) and osteocalcin expression was found in the fat fed, atherogenic susceptible strain (Parhami et al 1999; Parhami et al 2001). Animal work also revealed that hyperlipidemia may lead to osteoporosis via an increase in osteoclastic bone resorption (Tintut et al 2004). Prolonged treatment with high-density lipoprotein has also been shown to inhibit the osteogenic activity of calcifying vascular cells. Moreover, HDL inhibited the osteogenic activity induced by inflammatory cytokines (Parhami et al 2002).

Epidemiological evidence in humans examining the role of lipids in the relationship between CVD and osteoporosis remains controversial. For instance, there is evidence that hyperlipidemia (eg, elevated low-density lipoprotein) is associated with reduced bone mineral density (Yamaguchi et al 2002). However, abnormal lipid lipoprotein levels have also been shown to be associated with increased bone mineral density in humans (Adami et al 2004). Whereas, others have found no independent relationship between lipids and bone mineral density (Bagger et al 2007). For example, Bagger et al (2007) recently reported that there were no independent associations with lipid lipoprotein profile and bone mineral density of the hip or spine. Importantly, the authors also revealed that the severity of aorta calcification was independently associated with hip bone mineral density (with no contribution of lipids). The authors stated that these discrepancies provide evidence that the obstructive vascular disease (rather than lipid lipoproteins per se) facilitates the bone loss. The authors also postulated that lipids may act indirectly via the promotion of atherosclerosis which in turn can affect local bone metabolism. This effect is thought to be particularly evident at skeletal sites with end-arterial blood supply (Bagger et al 2007). This evidence supports the argument that a decrease in peripheral blood flow and supply could suppress bone cell function (Rubin and Silverberg 2004).

Endothelial function appears to be important for both vascular and bone health. The vascular endothelium provides a macromolecular barrier with multiple functions including: 1) anti-inflammation and pro-inflammation, 2) vasodilatation and vasoconstriction, 3) anti-thrombosis and pro-thrombosis, 4) anti-oxidation and pro-oxidation, and 5) growth inhibition and growth promotion (Whitney et al 2004). When the integrity of the endothelium is disrupted, as with oxidized LDL-C, an imbalance in these roles occurs resulting in endothelial dysfunction. Endothelial dysfunction is thought to be an obligatory first step in the process of atherosclerosis. Owing to the intimate contact with endothelial cells, the health of the endothelium appears to also be of great significance for bone health.

A healthy vascular tone is maintained by the continual release of low levels of nitric oxide (NO). NO is generated from L-arginine by NO synthase isoenzymes. Three NO synthase isoforms have been identified including a neuronal form (nNOS), an endothelial form (eNOS), and an inducible

form (iNOS). Recently, it has become apparent that NO is involved in the process of bone metabolism and as such the influence of NO on bone health has been the focus of several investigations. In bone, it has been established that nNOS is rarely expressed, while both eNOS and iNOS are expressed (Fox and Chow 1998). However, both the eNOS and nNOS isoforms affect bone differently. For instance, the eNOS isoform is expressed constitutively and is predominant in the osteoblast lineage (Fox and Chow 1998). Inflammation is associated with iNOS activity in osteoblast and osteoclast cells (Fox and Chow 1998; Armour et al 1999; Armour et al 2001b). For instance, Armour et al (2001b) revealed that the activation of the iNOS pathway contributes to inflammation-mediated osteoporosis via suppressed bone formation and osteoblast apoptosis. Osteoclasts have also shown low levels of eNOS and iNOS (Fox and Chow 1998). eNOS negative (knock-out) mice have demonstrated reduced bone volume, bone formation rates, BMD, and osteoblast numbers (Aguirre et al 2001; Armour et al 2001a; Samuels et al 2001). eNOS knock-out mice have also revealed a blunted response to exogenous estrogen, supporting the important role of eNOS in mediating the stimulatory action of estrogen on bone formation (Armour et al 2001a). Moreover, cells of osteoblast phenotype challenged with pulsatile fluid flow (as seen with exercise) have demonstrated increased eNOS production (Klein-Nulend et al 1998). Researchers have also shown that L-arginine administration prevented bone loss and bone collagen breakdown in cyclosporin A-treated rats (Fiore et al 2000).

These findings (from animal and cell culture models) indicate that NO may contribute to the osteogenic pathway. However, exactly how eNOS and iNOS contribute to bone health remains to be determined, especially in humans. Prospective human investigations have evaluated NO and bone (Jamal et al 1998; Nabhan 2006). For instance, Jamal et al (1998) revealed that intermittent nitrate use increased hip and heel BMD compared to non-users. However, there was no difference in fracture free survival between groups. A recent randomized controlled trial (Nabhan 2006) revealed that isosorbide mononitrate (a NO donor) was effective in reducing a marker of bone resorption (urine N-telopeptide) and increasing a marker of bone formation (alkaline phosphatase) in post-menopausal women. The authors postulated that a NO donor may be effective in the prevention of post-menopausal osteoporosis. Additional research is required to clearly identify the roles that the specific NO isoforms have on bone health.

Other factors involved in arterial wall calcification have also been implicated in the relationship between CVD and osteoporosis. Potential factors include (but are not exclusive to) osteopontin, matrix Gla-proteins and osteocalcin, and leptin. It is recommended that interested readers consult reviews on this topic (Doherty et al 2003; Hamerman 2005; Rajzbaum and Bezie 2006) for further information regarding the varied potential mechanisms explaining the relationship between CVD and osteoporosis.

Based on the above literature it is apparent that multiple pathophysiological mechanisms can be responsible for the observed relationship between CVD and osteoporosis. It is however important to note that many of the above findings provide evidence that vascular dysfunction plays a key role in the association between CVD and osteoporosis. Thus, impaired blood flow and a diseased vascular system may have negative effects on bone health, or diseased bone may impair vascular health (Whitney et al 2004).

Differences between men, pre- and postmenopausal women

It is important to discuss the differences between men and women across the lifespan with respect to the risk for and prevalence of CVD and osteoporosis. Often CVD is thought to be a disease of primary concern for men and osteoporosis of primary concern for women owing to the differential prevalence rates for each condition amongst sexes. However, these statements must be tempered greatly owing to the unique sex-based differences in each condition.

With respect to CVD, men are more prone to atherosclerosis (approximately 3–4 fold greater) than women (Eaker et al 1993, American Heart Association 2006). With aging, this ratio declines to approximately 2 between the ages of 65–69, and to 1 by the age of 85 (Eaker et al 1993). The incidence of CVD increases markedly in women after menopause (Witteman et al 1989). It has been estimated that the coronary heart disease rates increase 2–3 fold after menopause in women (increasing with aging) (American Heart Association 2006). Recent American data indicates that the prevalence of coronary heart disease in women 75 years or older was 10.3% in comparison to 1.6% between the ages of 45–54 (American Heart Association 2006).

The majority of sudden cardiac deaths occur in men (approximately 3–4 fold greater incidence); however, this inequality is also reduced with advancing age (American Heart Association 2006). Men have been shown to have a higher blood pressure than women until approximately age 45; thereafter, women have a higher blood pressure (American Heart Association 2006). This sex-based

difference appears to be particularly pronounced in the elderly. For instance, in the United States the prevalence of hypertension is approximately 34% for both men and women aged 45–64. However, in the 75%+ cohort women have an increased prevalence of high blood pressure than men (83 vs 69%, respectively) (American Heart Association 2006). Although men (under the age of 75) have greater prevalence of coronary heart disease, women have a greater prevalence of CVD events due to heart failure (American Heart Association 2006).

The death rates associated with a myocardial infarction appear to be higher in women than men (Greenland et al 1991; Gottlieb et al 2000). For instance, in the United States, 25% of men and 38% of women die within one year after have an initial myocardial infarction (American Heart Association 2006). This may be in part due to the fact that women are often older when they have a myocardial infarction. More American women (64%) than men (50%) who die suddenly due to CVD had no previous symptoms (American Heart Association 2006).

There is an increased incidence of osteoporosis in women (approximately 80%) (National Osteoporosis Foundation 2007). The incidence of osteoporosis increases markedly after the age of menopause with approximately 1 in 4 women over the age of 50 exhibiting osteoporosis (Osteoporosis Canada 2007). This has led to a primary focus on elderly women in research within the field; however, approximately 30% of hip fractures occur in men. Men also have a higher risk of dying after a fracture (Center et al 1999). It has been estimated that the mortality rate in the first year after a fracture in men is twice that of women (Wright 2006).

Risk management of cardiovascular disease and osteoporosis

With the projected progressive increase in life expectancy it is clear that the incidence of both CVD and osteoporosis will increase for both males and females. Therefore, effective preventive interventions are required to offset the inevitable burden these chronic conditions will place upon society. It is also important to note, that with the global increase in life expectancy a major challenge for public health care systems will be the enhancement of overall quality of life, and not solely the prevention of chronic disease. Life expectancy does not take into account the years a person may live in a dependent or diseased state. Since overall quality of life is of utmost importance (especially as one ages) recent health agencies (such as the World Health Organization) have adopted new criteria to determine the number of years a person might live in a healthy state. For instance, the World Health Organization has recently introduced the Health-Adjusted Life Expectancy (HALE) scale that takes into account the anticipated years of ill-health to provide an estimate of years of healthy living (Figure 2).

Health-related quality of life includes physiological, functional, emotional and spiritual well-being. We have discussed previously the physiological determinants of chronic disease. However, a holistic approach to health care should also include the evaluation of the other determinants of health-related quality of life. For instance, emotional and spiritual well-being are key factors in maintaining a high quality of life across the lifespan (Warburton et al 2001a, 2001b). Moreover, the maintenance of functional capacity is fundamental to healthy aging (Warburton et al 2001a, 2001b). Functional independence, especially as one ages, is related largely to one's ability to perform activities of daily living. In fact, the capacity to carry out activities of daily living is thought to be of greater concern to the elderly than chronic disease (Ensrud et al 1994; Warburton et al 2001a, 2001b, 2006a). Therefore, preventative strategies should be developed that not only specifically target individual risk factors for chronic disease, but also address the emotional, physical and social well-being of the individual (Warburton et al 2001a, 2001b; Palacios et al 2005).

It is essential to stress that preventative strategies for both CVD and osteoporosis should not focus solely on the elderly at the expense of younger generations (Center et al 1999). It is clear that CVD starts in childhood and progresses with advancing age. It has been estimated that approximately one half of North American children exhibit one or more risk factor for CVD, with up to a third exhibiting at least one risk factor by the time they enter elementary school (Freedman et al 1999). In fact, many children and adolescents exhibit multiple risk factors for CVD (Troiano et al 1995; Berenson et al 1998; McGill et al 2000). As discussed previously, we have recently shown that 8% of elementary children had four or more CVD risk factors (McKay et al 2004). This is of concern owing to the fact that the severity of underlying cardiovascular disease is greater with increasing numbers of CVD risk factors (Berenson et al 1998) and these children may be more likely to develop CVD in adulthood (Reid et al 1999). Moreover, childhood and adolescence are important periods for the development of bone health. In fact, approximately 90% of adult bone

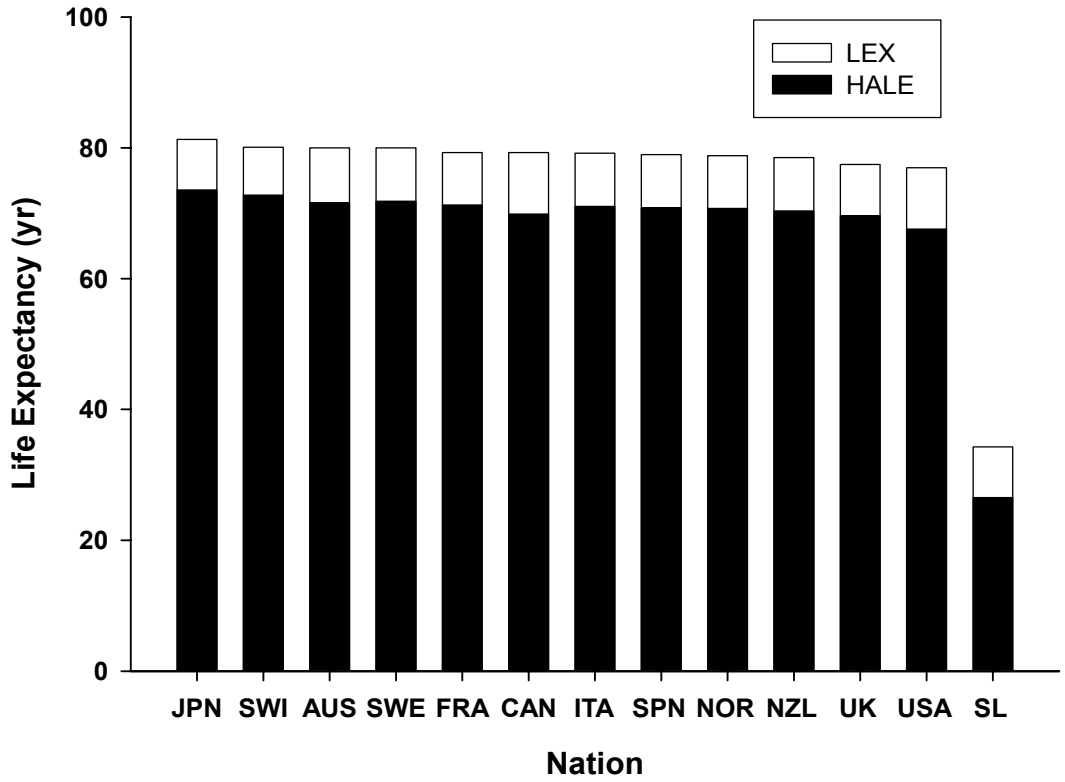

Figure 2 Life expectancy and health-adjusted life expectancy in representative nations.
Abbreviations: LEX, Life Expectancy; HALE, Health-Adjusted Life Expectancy; JPN, Japan; SWI, Switzerland; AUS, Australia; SWE, Sweden; FRA, France; CAN, Canada; ITA, Italy; SPN, Spain; NOR, Norway; NZL, New Zealand; UK, United Kingdom; USA, United States of America; SL, Sierra Leone.
The Health-Adjusted Life Expectancy (HALE) Takes into account the years of ill-health, weighted according to severity, and subtracted from the anticipated life expectancy to provide the equivalent years of healthy life.
Source: World Health Organization, World Health Report 2001. http://www3.who.int/whosis/hale/hale.cfm?path=whosis,hale&language=english (World Health Organization 2001).

mass is accrued by the end of adolescence (McKay et al 2005). Effective interventions (in particular interventions involving mechanical loading) can have marked effects upon bone metabolism and health during the growing years (McKay et al 2005). For instance, exercise interventions have been shown to have a greater effect when started in premenarche compared to postmenarche (Kannus et al 1995). It appears that benefits derived from interventions that optimize peak bone mass (such as weight-bearing exercise) may extend into adulthood (Khan et al 2000). Therefore, preventative interventions must be devised that meet the needs of individuals from across the lifespan.

We feel that a preventative model across the lifespan is required to effectively address the high prevalence of CVD and osteoporosis, and to improve overall quality of life. Given the interrelationships between multiple chronic disease states a holistic approach to medicine should be advocated. In short, rather than focusing on the prevention and treatment of single disease states we should consider the treatment of the whole patient. Physical activity interventions have shown this strategy will hold great potential for addressing concurrently multiple chronic diseases, while improving overall quality of life.

Does minimizing the risk in one disease predispose an individual to risk in the other?

As discussed above, effective interventions can concurrently target multiple modifiable risk factors for both CVD and osteoporosis. For instance, the cessation of smoking and an increase in weight-bearing physical activity would each have a beneficial effect on both chronic conditions. However, clinicians must be aware that there is the potential for the reduction of risk in one disease to predispose the individual to an increased risk for the other condition. Perhaps the best example of this is weight reduction for the treatment of CVD. This is owing to the fact that a low BMI is an independent predictor of the risk for osteoporosis (De Laet et al 2005). For instance, De Laet et al (2005) revealed that a BMI of 20 kg/m^2 was associated with a

2-fold increase in the risk for hip fracture in comparison to a BMI of 25 kg/m^2. The risk for hip fracture however does not appear to be linear across BMI levels, as a BMI of 30 kg/m^2 only conferred a 17% reduction in hip fracture risk in comparison to a BMI of 25 kg/m^2. It appears that weight loss is also associated with an increased risk for osteoporosis (Ensrud et al 2005; Macdonald et al 2005). Macdonald et al (2005) recommended that postmenopausal women (who are not taking hormone-replacement therapy) should be informed that low body weight or losing weight may worsen the degree of bone loss. Therefore, although losing weight confers health benefits for CVD, it may be counterproductive for osteoporosis. However, the level of weight loss often achieved in patients with CVD after lifestyle and/or pharmacological interventions is often not excessive and as such may confer limited additional risk for the development of osteoporosis. In fact, given the apparent relationship between CVD and osteoporosis it is likely that the changes in vascular health would be of great health benefit to the individual patient. It is important to note, that there are interventions (such as physical activity) that can meet the needs of both chronic conditions without markedly compromising the cardiovascular or skeletal health. This is particularly salient given the beneficial exercise-associated changes in bone and vascular health.

Hormone replacement therapy

Postmenopausal hormone therapy has been widely advocated for the prevention of osteoporosis and the treatment of postmenopausal symptoms (Brown and Josse 2002). It was also anticipated that estrogen replacement therapy or combined estrogen-progestin therapy (hormone replacement therapy) would lower CVD risk (Alexandersen et al 2006). In fact, during the early 1990s hormone therapy was widely promoted as an effective primary and secondary preventive strategy against CVD (Rossouw 2005). This was based largely on epidemiological (observational) studies that demonstrated a beneficial effect of hormone replacement therapy on risk factors and outcomes for CVD (Stampfer et al 1991; Grodstein et al 1996). However, the results of hormone replacement therapy clinical trials have had conflicting effects with respect to the risk for CVD. For instance, the Heart and Estrogen/Progestin Replacement Studies (HERS I and II) (Hulley et al 1998; Grady et al 2002) and the Women's Estrogen for Stroke Trial (WEST) (Viscoli et al 2001) did not show a reduction in the incidence of CVD. Moreover, the Women's Health Initiative (WHI) terminated early the trial of estrogen plus progestin owing to increased risks of breast cancer and cardiovascular events (Rossouw et al 2002). Recently, Alexandersen et al (2006) revealed that 2–3 years of hormone replacement therapy does not increase all-cause mortality and may lead to cardiovascular health benefits (including decreased severity of aortic calcification). Owing to the discrepancies in the field, it is apparent that hormone replacement therapy should be used cautiously considering the risk benefit ratio for each individual patient.

Priority: Cardiovascular disease versus osteoporosis

Physicians and health care professionals are often met with the challenge of assessing and managing the risk of individuals with varied medical conditions (such as multiple chronic diseases). In terms of screening and risk management osteoporosis is often considered to be of lower priority than cardiovascular disease.

While the incidence of CVD-related mortality and morbidity is shown to be greater than that for osteoporosis, the importance of preventing and treating osteoporosis cannot be discounted. As discussed previously, osteoporosis affects a significant proportion of society (in particular elderly women). Further, as the population ages, these numbers are expected to increase substantially (Tucci 2006). The economic and societal implications of osteoporosis are considerable owing to the significant morbidity, mortality, and health care costs associated with osteoporotic fractures (Sasser et al 2005; Mauck and Clarke 2006). According to Sasser et al (2005), in the United States alone, the average annual direct costs of osteoporosis per patient is $6,259 while the indirect cost associated with the disease is $4,039 demonstrating a significant financial burden. Therefore, overcoming the challenge of providing optimal health care while managing the costs associated with treatment is of great concern (especially as the population ages) (Mauck and Clarke 2006; Tucci 2006). Tucci (2006) suggests that in order to control costs, post-fracture care and identification of individuals with an increased risk of fracture may enable cost-effective management and treatment of osteoporosis. It is therefore necessary to ensure effective preventative measures and treatment protocols in order to reduce the number of individuals at risk of developing osteoporosis and experiencing an osteoporosis-related fracture (Tucci 2006).

Fortunately, exercise interventions can help address both CVD and osteoporosis concurrently, thereby limiting the need for clinicians to prioritize between conditions. In fact, it is likely that primary and secondary prevention

through healthy lifestyle interventions may serve to decrease the physical, social, emotional and spiritual impairments to the individual as well as decrease the direct and indirect medical costs associated with the treatment of both conditions.

Physical activity and its role in the prevention of CVD and osteoporosis

Physical inactivity is a major risk factor for both osteoporosis and CVD (Warburton et al 2006a, 2006b). There is also extensive literature indicating that physical activity is an effective primary and secondary preventive strategy against CVD, osteoporosis, and multiple other chronic diseases (including obesity, stroke, hypertension, type 2 diabetes, colon cancer, breast cancer, and several psychological disorders) (Warburton et al 2006a).

Being fit or physically active has been shown to lead to a 30%–50% reduction in the risk of death from any cause and from CVD (Warburton et al 2006a). Low maximal aerobic fitness is as important a risk factor for premature mortality as is overweight and obesity (Blair and Brodney 1999). Several mechanisms may explain the reduced premature mortality rates and incidence of CVD in individuals who are habitually active (Warburton et al 2006a, 2006b). For instance, regular aerobic exercise has been shown to improve body composition (via reduced abdominal adiposity and/or improved weight control) (Tremblay et al 1990; Seidell et al 1991; Slattery et al 1992; Maiorana et al 2003), enhance lipid lipoprotein profiles (including increased HDL-cholesterol, reduced triglycerides, and decreased LDL-cholesterol) (Taimela et al 1994; Halle et al 1996; Berg et al 1997), improve glucose homeostasis (Wallberg-Henriksson et al 1998; Kelley and Goodpaster 1999), decrease blood pressure (American College of Sports Medicine 1993; Warburton et al 2006a), reduce systemic inflammation (Adamopoulos et al 2001), enhance cardiac function (Warburton et al 1999, 2004a, 2004b), and improve endothelial function (Gokce et al 2002; Hambrecht et al 2003; Kobayashi et al 2003).

Particularly relevant to this discussion is the exercise-mediated changes in vascular health and endothelial function. Several studies have evaluated the effects of habitual exercise on endothelial function in elderly and patient populations. Cross-sectional investigations have revealed that active older adults have improved vascular health in comparison to sedentary individuals (Taddei et al 2000; McKechnie et al 2001; Galetta et al 2006a). Moreover, habitual physical activity appears to attenuate the age-associated decline in endothelial function (Taddei et al 2000; Galetta et al 2006a, 2006b). Research trials have also revealed the ability of exercise interventions to improve vascular health and endothelial function in asymptomatic and symptomatic populations (Hambrecht et al 1998, 2000, 2003; Gokce et al 2002; Kobayashi et al 2003) (with the beneficial adaptations being particularly apparent in clinical populations (Green et al 2004)).

A direct relationship exists between lifetime physical activity and bone health. In particular, weight-bearing exercise appears to have a great effect on bone mineral density (Warburton et al 2001a, 2001b, 2006a). For instance, adults performing repetitive, high-intensity, weight-bearing exercise consistently have greater BMD than sedentary individuals (Bassey and Ramsdale 1994; Heinonen et al 1995; Lohman et al 1995; Warburton et al 2001a, 2001b). Prospective studies in post-menopausal women using weight bearing activity have often reported an increase or maintenance of total body, hip, and lumbar spine bone mineral density (Hatori et al 1993; Welsh and Rutherford 1996; Kohrt et al 1997). In fact, resistance training often results in site-specific and load-dependent improvements in BMD (Smidt et al 1992; Kerr et al 1996; Kohrt et al 1997; Warburton et al 2001a, 2001b). A meta-analysis of randomized controlled trials reported that exercise training interventions result in the prevention or reversal of approximately 1% of bone loss per year in the lumbar spine and femoral neck in both pre- and post-menopausal women (Wolff et al 1999). Moreover, exercise training has been shown to reduce the risk and number of falls (Tinetti et al 1994; Wolf et al 1996; Shaw and Snow 1998; Carter et al 2001a, 2001b; Liu-Ambrose et al 2004a) and fractures (Stevens et al 1997; Joakimsen et al 1998; Gregg et al 2000; Kujala et al 2000). Preliminary evidence also indicates that routine physical activity is effective in improving bone density in older women with low bone mineral density (Liu-Ambrose et al 2004b).

It is clear that regular physical activity prolongs one's lifespan (Lee et al 1997), but it also delays greatly the onset of chronic disease and/or disability. Therefore, physical activity is an effective means to increase the number of years that a person lives in a healthy state, thereby minimizing the years spent in a dependent state. If disability does occur it is generally for a short period of time at the end of life (Powell and Blair 1994). This is particularly important with the ever-increasing aging population.

Summary

It is clear that both CVD and osteoporosis are major health burdens affecting millions of people globally. A growing

body of research supports a direct association between CVD and osteoporosis providing an explanation for why (in part) individuals often exhibit both chronic conditions. There are numerous factors that may account for this relationship including risk factors that are common to both debilitating chronic conditions, and varied pathophysiological mechanisms. Both chronic conditions share similar modifiable risk factors (including physical inactivity) and such effective treatment strategies can be developed to address both diseases.

There appear to be distinct differences between (and within) sexes across the lifespan with respect to each chronic condition that need to be considered when treating the individual patient. It is important to have an understanding of the effects of varied primary and secondary preventative strategies on multiple chronic conditions. Preventative strategies should not only target individual risk factors for chronic disease, but also address the overall health-related quality of life of the individual. We advocate a holistic approach to the prevention and treatment of these chronic debilitating diseases; an approach that considers the social, emotional, spiritual and physical well-being of the individual.

When designing an intervention (such as a physical activity intervention) to address both chronic conditions, clinicians must be able to balance the risk of each condition. Clinicians must be aware that there is a potential for the risk reduction in one disease to predispose the individual to an increased risk for the other condition. With this knowledge, clinicians will be able to develop effective interventions that attenuate the risk while addressing the specific limitations of each chronic condition.

Although CVD takes a higher toll on society in terms of premature mortality, morbidity rates, and health care costs, the importance of the prevention/treatment of osteoporosis (particularly in elderly women) can not be overlooked. Habitual physical activity is an effective primary and secondary preventative strategy for both chronic conditions across the lifespan. Training-induced adaptations in endothelial function appear to be particularly important for the concurrent reductions in the risk of CVD and osteoporosis.

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