

Hyperlipidemia

Definition:

Hyperlipidemia, hyperlipoproteinemia or dyslipidemia is the presence of elevated or abnormal levels of lipids and/or lipoproteins in the blood (*National Cholesterol Education Program- Adult treatment panel III; NCEP-ATPIII, 2002*).

Classification:

1- Primary hyperlipidemias: are classified according to the **Fredrickson classification** which is based on the pattern of lipoproteins on electrophoresis or ultracentrifugation (*Frederickson and Lee, 1965*).

Table (1): Classification of hyperlipidemia

Hyperlipopr oteinemia	Synonyms	Problems	Labs description
Type I	Buerger-Gruetz syndrome, Primary hyperlipoproteinaemia, or Familial hyperchylomicronemia	Decreased lipoprotein lipase (LPL) or altered ApoC2	Elevated Chylomicrons
Type IIa	Polygenic hypercholesterolaemia or Familial hypercholesterolemia	LDL receptor deficiency	Elevated LDL only
Type IIb	Combined hyperlipidemia	Decreased LDL receptor and Increased ApoB	Elevated LDL and VLDL and Triglycerides
Type III	Familial	Defect in	Increased IDL

	Dysbetalipoproteinemia	ApoE synthesis	
Type IV	Endogenous Hyperlipemia	Increased VLDL production and Decreased elimination	Increased VLDL
Type V	Familial Hypertriglyceridemia	Increased VLDL production and Decreased LpL	Increased VLDL and Chylomicrons

(Frederickson and Lee, 1965)

LDL: low density lipoprotein VLDL: very low density lipoprotein

IDL: intermediate density lipoprotein LpL: lipoprotein lipase

Hyperlipoproteinemia type I:

This very rare form (also known as Buerger-Gruetz syndrome, primary hyperlipoproteinaemia, or familial hyperchylomicronemia) is due to a deficiency of LPL or altered apolipoprotein C2, resulting in elevated chylomicrons, the particles that transfer fatty acids from the digestive tract to the liver. Its prevalence is 0.1% of the population (*NCEP-ATPIII, 2002*).

Hyperlipoproteinemia type II:

Hyperlipoproteinemia type II, by far the most common form, is further classified into type IIa and type IIb, depending mainly on whether there is elevation in the triglyceride level in addition to LDL cholesterol (*NCEP-ATPIII, 2002*).

***Type IIa:**

This may be sporadic (due to dietary factors), polygenic, or truly familial as a result of a mutation either in the LDL receptor gene on chromosome 19 (0.2% of the population) or the ApoB gene (0.2%). The familial form is characterized by tendon xanthoma, xanthelasma and premature cardiovascular disease (*NCEP-ATPIII, 2002*).

***Type IIb:**

The high VLDL levels are due to overproduction of substrates, including triglycerides, acetyl CoA, and an increase in B-100 synthesis. They may also be caused by the decreased clearance of LDL. Prevalence in the population is 10% (*NCEP-ATPIII, 2002*).

Hyperlipoproteinemia type III:

This form is due to high chylomicrons and IDL. Also known as broad beta disease or dysbetalipoproteinemia, the most common cause for this form is the presence of ApoE E2/E2 genotype. It is due to cholesterol-rich VLDL (β -VLDL). Prevalence is 0.02% of the population (*NCEP-ATPIII, 2002*).

Hyperlipoproteinemia type IV:

This form is due to high triglycerides. It is also known as hypertriglyceridemia (or pure hypertriglyceridemia). Prevalence is about 16% of adult population (*NCEP-ATPIII, 2002*).

Hyperlipoproteinemia type V:

This type is very similar to type I, but with high VLDL in addition to chylomicrons (*NCEP-ATPIII, 2002*).

Unclassified forms:

Non-classified forms are extremely rare (*NCEP-ATPIII, 2002*):

- Hypo-alpha lipoproteinemia
- Hypo-beta lipoproteinemia (prevalence 0.01-0.1%).

2- Secondary hyperlipidemia: The secondary hyperlipidemia is caused by a diet high in total fat, saturated fat, or cholesterol, obesity, diabetes, hypothyroidism, kidney problems, Cushing's syndrome, and certain drugs, such as contraceptive pills, beta-blockers, and cortisone drugs (*Stone, 1994*).

Significance of hyperlipidemia:

Lipid and lipoprotein abnormalities are extremely common in the general population, and are regarded as a highly modifiable risk factor for cardiovascular disease due to the influence of cholesterol, one of the most clinically relevant lipid substances, on atherosclerosis. In addition, some forms may predispose to acute pancreatitis (*NCEP-ATPIII, 2002*).

In adults, LDL is strongly associated with a higher risk, and HDL is associated with a lower risk, of coronary heart disease (CHD). Lowering lipids through dietary or pharmacological therapy has been shown to decrease the incidence of atherosclerotic events. The extent of abnormal lipids and other cardiovascular risk factors during childhood and adolescence is related to the severity of atherosclerosis (*Shamir and Fisher, 2000*).

Adolescents with “high” total cholesterol or LDL may have a genetic disorder of lipid metabolism such as familial hypercholesterolemia or familial combined hypercholesterolemia. Those

with homozygous forms of these disorders can experience myocardial infarction or other events during childhood or early adolescence. Familial hypercholesterolemia is often diagnosed in adolescence and is characterized by high LDL levels that can be refractory to dietary treatment. These patients can present clinically with xanthomas or xanthelasma— cholesterol deposits under the skin on the hands, elbows, knees, heel or eyelids (*Lipman et al., 2000*).

Treatment:

While dietary modification is the initial approach, many patients require treatment with statins (3-hydroxy-3-methylglutaryl coenzyme A ;HMG-CoA reductase inhibitors) to reduce cardiovascular risk. If the triglyceride level is markedly raised, fibrates may be preferable due to their beneficial effects. Combination treatment of statins and fibrates, while highly effective, causes a markedly increased risk of myopathy and rhabdomyolysis and is therefore only done under close supervision. Other agents commonly added to statins are ezetimibe, niacin and bile acid sequestrants. There is some evidence for benefit of plant sterol-containing products and ω_3 -fatty acids (*Thompson, 2004*).

Obesity

Definition:

Obesity can be defined in absolute or relative terms. In practical settings, obesity is typically evaluated in absolute terms by measuring BMI (body mass index), but also in terms of its distribution through waist circumference or waist-hip circumference ratio measurements. In addition, the presence of obesity needs to be regarded in the context of other risk factors and co-morbidities (*National Institutes of Health; NIH, 2000*).

BMI:

BMI, or body mass index, is a simple and widely used method for estimating body fat (*Mei et al., 2002*). It is calculated by dividing the subject's weight by the square of his/her height, typically expressed either in metric or US "Customary" units:

Metric: $BMI = kg / m^2$

Where ***kg*** is the subject's weight in kilograms and ***m*** is the subject's height in metres.

US/Customary: $BMI = lb \times 703 / in^2$

Where ***lb*** is the subject's weight in pounds and ***in*** is the subject's height in inches.

The current definitions commonly in use establish the following values, agreed in 1997 and published in 2000 (*World Health Organization; WHO, 2000*).

- A BMI less than **18.5** is *underweight*
- A BMI of **18.5–24.9** is *normal weight*
- A BMI of **25.0–29.9** is *overweight*
- A BMI of **30.0–39.9** is *obese*
- A BMI of **40.0 or higher** is *severely (or morbidly) obese*
- A BMI of **35.0 or higher** in the presence of at least one other significant comorbidity is also classified by some bodies as *morbid obesity*.

Waist circumference:

Increasing understanding of the biology of different forms of adipose tissue has shown that *visceral* fat or *central obesity* (male-type or apple-type obesity) has a much stronger correlation, particularly with cardiovascular disease, than the BMI alone (*Yusuf et al., 2004*).

The absolute **waist circumference** *>102 cm* in *men* and *>88 cm* in *women* or **waist-hip ratio** *>0.9* for *men* and *>0.85* for *women* (*Yusuf et al., 2004*). are both used as measures of central obesity.

Body fat measurement:

Two simpler methods for measuring body fat are the *skinfold test*, in which a pinch of skin is precisely measured to determine the thickness of the subcutaneous fat layer; or *bioelectrical impedance analysis*, usually only carried out at specialist clinics (*National Institute of Health and Clinical Excellence; NICE, 2006*) .

Effects on health:

obesity is also correlated with a variety of other complications. For some of these complaints, it has not been clearly established to what extent they are caused directly by obesity itself, or have some other cause (such as limited exercise) that causes obesity as well (*Zagorsky, 2004*):

- *Cardiovascular*: congestive heart failure, enlarged heart and its associated arrhythmias, and pulmonary embolism
- *Endocrine*: polycystic ovarian syndrome (PCOS), menstrual disorders, and infertility
- *Gastrointestinal*: gastroesophageal reflux disease (GERD), fatty liver disease, cholelithiasis (gallstones), and colorectal cancer
- *Renal and genitourinary*: erectile dysfunction, urinary incontinence, and hypogonadism (male)
- *Musculoskeletal*: hyperuricemia (which predisposes to gout), immobility, osteoarthritis, low back pain
- *Neurologic*: stroke, headache, carpal tunnel syndrome, dementia
- *Respiratory*: dyspnea, obstructive sleep apnea, hypoventilation syndrome, asthma
- *Psychological*: Depression, body dysmorphic disorder.

Causes and mechanisms:***Lifestyle**

Dietary intake and sedentary lifestyle has a significant role to play (*Lin et al.,1999*).

***Genetics**

A 2007 study identified fairly common mutations in the *FTO* gene; heterozygotes had a 30% increased risk of obesity, while homozygotes faced a 70% increased risk (*Frayling et al., 2007*).

***Medical illness**

Medical illnesses that increase obesity risk include hypothyroidism, Cushing's syndrome, growth hormone deficiency (*Rosén et al., 1993*).

Treatment:

In a clinical practice guideline by the *American College of Physicians* (*Snow et al., 2005*) the following recommendations are made:

1. People with a BMI of over 30 should be counseled on diet, exercise and other relevant behavioral interventions, and set a realistic goal for weight loss.
2. If these goals are not achieved, pharmacotherapy can be offered. Drug therapy may consist of sibutramine, orlistat, phentermine, diethylpropion, fluoxetine, and bupropion. For more severe cases of obesity, stronger drugs such as amphetamine and methamphetamine may be used on a selective basis. Evidence is not sufficient to recommend sertraline, topiramate, or zonisamide.
3. In patients with BMI > 40 who fail to achieve their weight loss goals (with or without medication) and who develop obesity-related complications, referral for bariatric surgery may be indicated.

HYPERTENSION

Definition and classification:

Hypertension is defined conventionally as blood pressure $\geq 140/90$ mmHg. This serves to characterize a group of patients who carry a risk of hypertension-related cardiovascular disease that is high enough to merit medical attention (*Kaplan, 2001*). However, *Black, (1999)* reported that the risk of fatal and non fatal cardiovascular disease in adults is lowest with systolic blood pressure of less than 120 mmHg and diastolic of less than 80 mmHg. Many clinical trials classify hypertension according to the diastolic blood pressure. From these clinical classification the seventh report of the *Joint National Committee (JNC, 2003)* classifications which is based on the level of systolic and/or diastolic pressure and is summarized in (Table 2).

Table (2): Classification of hypertension:

Category	Blood pressure (mmHg)		
	Systolic		Diastolic
Normal	< 120	and	< 80
Prehypertension:	130-139	or	85-89
Stage 1 hypertension	140-159	or	90-99
Stage 2 hypertension	≥ 160	or	≥ 100

(*JNC, 2003*)

Types of hypertension: (Table 3)

I- Systolic and diastolic hypertension:

a- Primary, essential, or idiopathic

b- Identifiable (secondary) hypertension:

Renal:

- Renal parenchymal disease
 - Acute glomerulonephritis
 - Chronic nephritis
 - Diabetic nephropathy
- Renovascular
 - Renal artery stenosis
 - Intrarenal vasculitis

Endocrine:

- Acromegaly
- Hypothyroidism
- Hyperthyroidism
- Hypercalcemia (hyperparathyroidism)
- Adrenal
 - Cushing's syndrome
 - Primary aldosteronism
 - Pheochromocytoma

Pregnancy- induced hypertension :

Neurological disorders :

- Increased intracranial pressure
- Brain tumor
- Encephalitis

Others:

- Acute stress, including surgery
- Hypoglycemia
- Burns
- Pancreatitis
- Alcohol withdrawal
- Increased intravascular volume
- Alcohol and drug abuse

II- Isolated systolic hypertension:

Increased cardiac output

- Aortic valvular insufficiency
- Arteriovenous fistula
- Thyrotoxicosis

Rigidity of the aorta

(Grassi et al. 1998)

Risk stratification:

The risk for the cardiovascular disease in patients with hypertension is determined not only by the level of the blood pressure but also by the presence or absence of target organ damage (TOD) or other risk factors such as smoking, hyperlipidemia, and diabetes, as shown in table (4) (*JNC, 2003*):

Table (4): Cardiovascular risk factors

Major risk factor:	
	Hypertension
	Cigarette smoking
	Obesity
	Physical inactivity
	Hyperlipidemia
	Diabetes Mellitus
	Microalbuminuria
	Age (> 55 years for men, > 65 years for women).
Target organ damage:	
Heart	
	Left ventricular hypertrophy
	Angina or prior myocardial infarction
	Heart failure.
Others	
	Stroke or transient ischemic attack
	Chronic kidney disease
	Peripheral arterial disease.

(*JNC, 2003*)

Drug therapy of hypertension:

The usual approach to patients with diastolic blood pressure in the range of 85 to 94 mmHg is to use non pharmacological therapy as low sodium diet, weight reduction, cessation of smoking, avoidance of alcohol or reduction of alcohol intake, removal of stress and/or learning to deal with stress, relaxation, exercise and potassium-enriched diet, may result in adequate control of hypertension in up to 40% of patients. As an

initial strategy, low saturated fat intake is often necessary because of co-existing hyperlipedemia which increases risk (*Macgregor et al., 1995*).

Rationally antihypertensive drugs can be classified according to their sites or mechanisms of action into (*JNC, 2003*):

Diuretics:

- 1- Thiazides and related agents (hydrochlorothiazides, chlorthalidone).
- 2- Loop diuretics (frusemides, bumetanide, ethacrynic acid).
- 3- K⁺ sparing diuretics (amiloride, spironolactone).

Sympatholytic drugs:

- 1- Centrally acting agents (methyl dopa, clonidine, guanfacine, monoxidine and rilmenidine).
- 2- Adrenergic neurone blocking agents (guanethedine, reserpine).
- 3- β -adrenergic antagonists (propranolol, metoprolol....).
- 4- α -adrenergic antagonists (prazosin, terazosine...).
- 5- Mixed adrenergic antagonists (labetalol, carvedilol).

Vasodilators:

- 1- Arterial (hydralazine, minoxidil, diazoxide).
- 2- Arterial and venous (nitroprusside).

Ca⁺⁺ channel blockers (verapamil, nifedipine, amlodipine):

Angiotensin Converting Enzyme Inhibitors (ACEIs) (captopril, ramipril, and enalapril).

Angiotensin II-receptor Antagonists (Losartan, Valsartan and eprosartan).

Drug therapy of hypertension includes the use of one antihypertensive drug as a single agent or in combinations (*Kaplan, 1994*). ACE inhibitors, calcium antagonists and selective alpha-1 blockers, in addition to diuretics and Beta blockers, are increasingly recommended as first line therapy. Selection of initial therapy should take in account the limitations imposed by concomitant disorders and risk factors e.g. plasma lipids & diabetes mellitus (*Stamler et al., 1993*).

Table (5): Guidelines for selecting drug treatment of hypertension.

Clinical conditions that influence the choice of antihypertensive agents			
Disorder	Advantageous effect	Disadvantageous effect	Dangerous effect
Heart failure	Diuretics ACEIs	Ca ⁺⁺ -channel blockers	β-adrenoreceptor blockers
IDDM	ACEIs, α-blockers		Non-selective β blockers
NIDDM	ACEIs, α-blockers	Thiazides	
Hyperlipidaemia	ACEIs, α-blockers	Thiazides	Non-selective β blockers

(*Stamler et al., 1993*)

Obesity, hypertension, and weight reduction

When hypertensive patients are compared to normal, one of the major differences is an increase of prevalence of obesity (*Stanton et al., 1982*). Furthermore weight gain appears to be a main determinant of the rise in blood pressure that is commonly seen with aging (*Sonne-Holm et al., 1989*). In addition to the risk of hypertension, obesity further enhances total cardiovascular risk by increasing LDL levels, reducing HDL levels, and diminishing glucose tolerance (*Ostlund et al., 1990 and Laver et al., 1991*).

Effects of weight reduction:

The relation between obesity and hypertension is important clinically because weight loss can lead to significant fall in systemic blood pressure (*William, 1994*). This hypotensive response is associated with reduction in plasma volume and in plasma insulin and norepinephrine concentrations (*Reisin et al., 1983*). The decline in blood pressure induced by weight loss can occur in the absence of dietary sodium restriction; furthermore, modest sodium restriction (a decline in intake of 20 to 40 meq/day) may not produce an additive antihypertensive to that produced by weight reduction alone (*Satterfield et al., 1991*).

The diet-induced decline in blood pressure generally ranges from 0.3 to 1 mmHg for every 1 Kg of weight loss (*Steven and Ruth, 1993*). On the other hand, persistent obesity not only raises the blood pressure directly but also makes the hypertension more difficult to control by interfering with the efficacy of antihypertensive medications (*Modan et al., 1991*).

Reversal of obesity also may induce other beneficial effects:

- A fall in lipid levels, further decreasing cardiovascular risk associated with hypertension (*Oberman et al., 1990*).
- Partial reversal of left ventricular hypertrophy, which may occur independent of blood pressure level (*Himeno et al., 1996*).
- An improvement in patients sense of well-being and quality of life (*Wassertheil et al., 1991*).

Green tea (*Camellia sinensis*)

Description and Constituents:

Tea is one of the most widely consumed beverages in the world, second only to water, and its medicinal properties have been widely explored. The tea plant, *Camellia sinensis*, is a member of the Theaceae family, and black, oolong, and green tea are produced from its leaves. The leaves are dark green, alternate and oval, with serrated edges, and the blossoms are white, fragrant, and appear in clusters or singly (*Alschuler, 1998*).

Unlike black and oolong tea, green tea production does not involve oxidation of young tea leaves. Green tea is produced from steaming fresh leaves at high temperature, thereby inactivating the oxidizing enzymes and leaving the polyphenol content intact. The polyphenols found in tea are more commonly known as flavanols or catechins and comprise 30-40% of the extractable solids of dried green tea leaves. (*Alschuler, 1998*). The main catechins in green tea are epicatechin (EC), epicatechin-3-gallate (ECG), epigallocatechin (EGC), and epigallocatechin-3-gallate (EGCG), with the later being the highest in concentration. Green tea polyphenols have demonstrated significant antioxidant, anticarcinogenic, anti-inflammatory, thermogenic and antimicrobial properties in numerous human, animal, and in vitro studies. (*Graham, 1992*).

the level of caffeine was in the order in black tea > oolong tea > green tea > fresh tea leaf, but the levels of EGCG and total catechins were in the order in green tea > oolong tea > fresh tea leaf > black tea (*Lin et al., 2003*). Caffeine is present in green tea at an average level of 3% along with very small amounts of the other common methylxanthines, theobromine and theophylline (*Graham, 1992*).

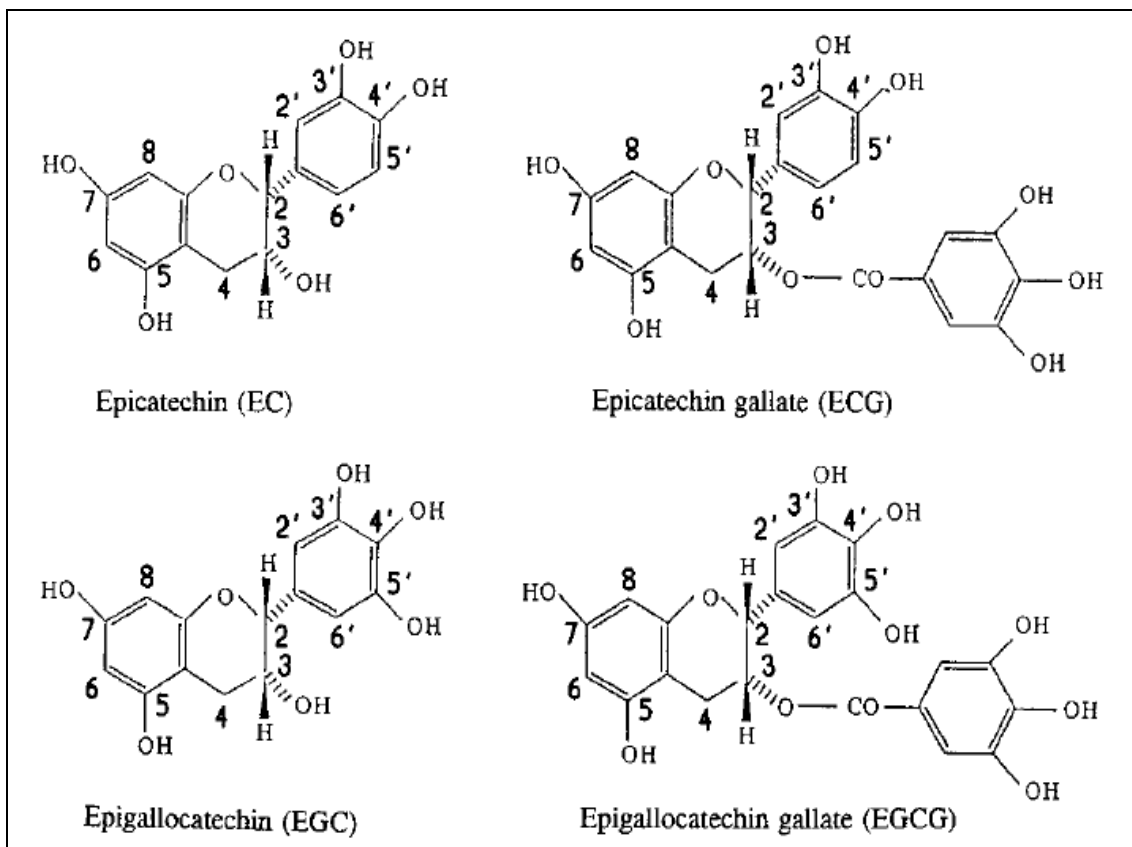


Figure (1) shows the major components of green tea (*Chan et al., 1999*)

Pharmacokinetics:

Following the administration of a single oral dose of green tea or decaffeinated green tea (20 mg/kg) or EGCG (2 mg/kg) to eight subjects, the plasma concentration time curves of the catechins were fitted in an one-compartment model. The maximum plasma concentrations of EGCG, EGC, and EC were 77.9, 223.4, and 124.03 ng/ml, respectively. The time needed to reach the peak concentrations was in the range of 1.3–1.6 h. The elimination half-lives were 3.4, 1.7, and 2 hrs, respectively.. In the plasma, EGCG was mostly present in the free form, whereas EGC and EC were mostly in the conjugated form. Over 90% of the total urinary EGC and EC, almost all in the conjugated forms, were excreted between 0 and 8 hrs (*Lee et al., 2002*).

At clinically relevant doses, the oral bioavailability of tea catechins was found to be low in animals and possibly in humans (*Cai et al., 2002*). *Chen et al. (1997)* reported that less than 2% EGCG was available in the systemic blood after oral administration in rats. When green tea catechins mixture was given to rats by intraportal infusion, high percentage of green tea catechins escaped first-pass hepatic elimination, with 87%, 108%, and 94.9% of EGCG, EGC, and EC, respectively, available in the systemic blood. This suggest that factors within the gastrointestinal tract such as limited membrane permeability or gut wall metabolism may contribute more significantly to the low oral bioavailability of green tea catechins (*Cai et al., 2002*).

Pharmacodynamics:

The polyphenols are believed to be responsible for most of green tea's roles in promoting good health (*Graham, 1992*):

Lipid metabolism:

Green tea catechins affect lipid metabolism by different pathways and prevent the appearance of atherosclerotic plaque. Green tea extract (GTE) intake decreases the absorption of triglycerides and cholesterol (*Loest et al., 2002 and Raederstorff et al., 2003*). Some studies reported that green tea catechins decrease plasma total cholesterol and blood triglycerides levels (*Tijburg et al., 1997, Miura et al., 2001 and Murase et al., 2002*). Green tea ingestion also decreases LDL cholesterol (*Yokozawa et al., 2002*) and increases HDL cholesterol, showing that green tea polyphenols exert an anti-atherosclerotic effect. This effect is also reported in apolipoprotein E-deficient mice (*Miura et al., 2001*).

These results demonstrate that long-term feeding of tea catechins can be beneficial in the suppression of high-fat diet-induced obesity by

modulating lipid metabolism. By this mechanism, green tea could possibly reduce the risk of associated diseases, including diabetes and coronary disease.

Carbohydrate metabolism:

In a study in rats treated with alloxan which destroys pancreatic cells, green tea extract (GTE) intake decreased serum glucose levels (*Sabu et al., 2002*) suggesting that catechins interact with glucose metabolism. Moreover, in an oral glucose tolerance test in normal rats, green tea catechins decreased plasma insulin levels but did not affect plasma glucose levels (*Wu et al., 2004*).

In type 2 diabetes, lipid metabolism is modified: plasma and liver triglyceride levels and plasma cholesterol levels are elevated. GTE intake reduced these values in both Zucker rats which are genetically obese and rats fed a sucrose-rich diet which induces obesity and insulin resistance (*Yang et al., 2001 and Hasegawa et al., 2003*).

Catechins also reduced plasma triglyceride levels in an oral glucose tolerance test in normal rats (*Wu et al., 2004*).

These results suggest that green tea catechins could act as preventive agents and could have a beneficial effect against lipid and glucose metabolism disorders implicated in type 2 diabetes.

Vascular disease:

Pathogenesis of vascular diseases such as atherosclerosis is 2 to 6 times higher in diabetic subjects than in normal subjects. Green tea catechins normalized the prostacyclin I₂/thromboxane A₂ (PGI₂/TXA₂) ratio in rats treated with streptozotocin and also suppressed phospholipase A₂ and cyclooxygenase activities (*Yang et al., 1999*).

These results show that green tea catechins have antithrombotic effects in these models.

Antioxidant markers and oxidant stress:

An imbalance between antioxidants and reactive oxygen species results in oxidative stress, leading to cellular damage. Catechins are hypothesized to help protect against these diseases by contributing, along with antioxidant vitamins (i.e., vitamins C and E) and enzymes [i.e., superoxide dismutase (SOD) and catalase], to the total antioxidant defense system. In vivo studies show that green tea catechins increase total plasma antioxidant activity (*Yokozawa et al., 2002 and Skrzydlewska et al., 2002*).

Intake of GTE also increases the activity of SOD in serum and the expression of catalase in the aorta (*Skrzydlewska et al., 2002 and Negishi et al., 2004*). This action is combined with direct action on oxygen species by a decrease in the nitric oxide plasma concentration (*Negishi et al., 2004*). Malon dialdehyde (MDA), a marker of oxidative stress, also decreases after green tea intake (*Yokozawa et al., 1999 and 2002*).

These results suggest that catechins could have a direct (antioxidant) or indirect (increase of activity or expression) effect.

Because catechins can act as antioxidants in vitro, they might prevent the oxidation of other antioxidants, such as vitamin E. However, ingestion of green tea catechins does not modify the plasma status of vitamins E and C in vivo (*Tijburg et al., 1997, Skrzydlewska et al., 2002 and Alessio et al., 2003*). One study (*Tijburg et al., 1997*) reports that catechins increase vitamin E concentration in LDL and in this way could protect LDL against peroxidation (*Yokozawa et al., 2002*).

Nephropathy:

Diabetes is generally accompanied by nephropathy due to microvascular dysfunction or impairment. In normal kidney tissue the production of TXA₂ and PGI₂ is controlled, and the balance between them is important to maintain homeostasis in vivo. A modification of the PGI₂/ TXA₂ ratio accelerates thrombogenesis in the renal tubules, increasing the risk of impaired function and atherosclerosis. The production of these compounds depends on the activity of phospholipase A2 (which is higher in the case of kidney disorders) and the fatty acid composition. Streptozotocin increases the synthesis of TXA₂ and decreases that of PGI₂. Administration of green tea catechins in rats pretreated with streptozotocin decreases the synthesis of TXA₂ and increases that of PGI₂ (*Rhee et al., 2002 a & b*) and so returns the ratio to that of untreated rats. Kidney function is improved by green tea catechin supplementation as a result of its antithrombogenic action, which in turns controls the arachidonic acid cascade system. This also demonstrates that the glomerular filtration rate is increased.

A study examined blood variables of glomerular filtration (protein excretion, glucose excretion, and blood nitrogen) in rats treated with cisplatin, a nephropathy inducer (*Yokozawa et al., 1999*). Because green tea did not affect the excretion of protein and glucose in urine, the blood nitrogen level was markedly decreased. Moreover, in the kidney, SOD and catalase activities were decreased and increased, respectively. Thus, green tea catechins appear to reduce oxidative stress in the kidney.

Absorption of ions:

Tea catechins can affect iron absorption, particularly in groups at risk of iron deficiency (*Samman et al., 2001 and Nelson & Poulter 2004*), but their effects on other ions are poorly defined. Green tea ingestion over a long period does not affect the apparent absorption of copper, in contrast to that of zinc, which decreases, and that of manganese, which increases (*Zeyuan et al., 1998*). However, catechin intake does not affect the plasma concentration of these ions (*Record et al., 1996*). Green tea catechins have the potential to affect absorption and metabolism of ions because flavonoids interact with a variety of metal ions (*Mira et al., 2002*).

Hormone metabolism:

At a high dose (5% of diet for 13 wk), green tea extract (GTE) induced a thyroid enlargement (goiter) in normal rats (*Sakamoto et al., 2001 and Satoh et al., 2002*). This high-level treatment modified the plasma concentrations of the thyroid hormones. However, drinking even a very high dietary amount of green tea would be unlikely to cause these types of effects.

Thermogenesis:

Green tea may have thermogenic properties not attributable to its caffeine content. In a randomized clinical trial controlling for caffeine intake (*Dulloo et al., 1999*), GTE increased the energy expenditure of ten healthy young men 24 hours after consumption and 24-hour urinary norepinephrine excretion increased by 40% during treatment. The investigators of this study suggest a potential role of tea in the control of body weight.

Drug-metabolizing enzymes:

Long-term ingestion of green tea increases uridine diphosphate-glucuronosyl transferase (UDP-GT) activity in rats (*Sohn et al., 1994, Bu-Abbas et al., 1995, and Maliakal et al., 2001*), and after being absorbed, catechins are metabolized by drug-metabolizing enzymes in various organs (*Okushio et al., 1999, Donovan et al., 2001*). Thus, the increased glucuronidation through UDP-GT induction is contributed to the anticarcinogenic effect of green tea by facilitating the metabolism of chemical carcinogens into inactive products that are readily excreted. The interaction between 2-amino-3-methylimidazol(4,5-f)quinoline (IQ; a precarcinogen that was originally detected in an extract of fried meat) and green tea catechin metabolism was examined (*Embola et al., 2001*). Green tea modifies IQ metabolism in rats, increasing the formation of IQ glucuronides, which are then excreted in the urine.

Moreover, protection against cancers induced by polycyclic aromatic hydrocarbons by green tea catechins may be due to the inhibition of their cytochrome P450 (CYP450) metabolism (*Crespy and Williamson, 2004*).

Cancer:

Evidence for the anticarcinogenic potential of tea polyphenols has been provided by numerous in vitro and experimental studies describing their action to bind directly to carcinogens, induce Phase II enzymes such as UDP-GT and inhibit heterocyclic amine formation. Molecular mechanisms, including catechin-mediated induction of apoptosis and cell cycle arrest, inhibition of transcription factors nuclear factor- κ B (NF- κ B) and activator protein-1 (AP-1) and reduction of protein tyrosine kinase

activity and mRNA expression have also been suggested as relevant chemopreventive pathways for tea (*Ahmad and Mukhtar , 1999*).

Some epidemiological studies also support a protective role of tea against the development of cancer. Studies conducted in Asia, where green tea is consumed frequently and in large amounts, tend to show a beneficial effect on cancer prevention (*Nakachi et al., 2000 and Yang et al., 2000*). Importantly, the chemopreventive effect of tea also varies by the specific type of cancer:

Mammary cancer:

The effects of green-tea catechins on mammary cancer were tested in 7,12-dimethylbenz[a]anthracene (DMBA)-treated female rats (*Hirose et al., 1997 and Tanaka et al., 1997*). Green tea or EGCG exhibited chemopreventive action on DMBA-induced mammary carcinogenesis only when given in the postinitiation stage, and the effect was not dose dependent. Indeed, green tea ingestion markedly reduced invasive tumors in rats with DMBA-induced mammary carcinogenesis (*Kavanagh et al., 2001*).

These results suggest that green tea could act as a preventive agent against mammary cancer postinitiation.

Liver cancer:

Animals treated with Diethylnitrosamine (DENa) and green tea at different concentrations showed a marked decrease in liver tumors (*Hirose et al., 1995, Cao et al., 1996, and Zhang et al., 2002*).

This suggests a possible association between the chemopreventive activity of tea on liver tumors and the concentration of EGCG in tea. In the same model, green tea reduced oxidative DNA damage in mice (*Tamura et al, 1997*) and rats (*Hasegawa et al, 1995 and Sai et al, 1998*). The authors suggest that green tea may be a chemopreventive agent for hepatocarcinogenesis. Moreover, daily ingestion of green tea

prevented hepatotoxicity and cell proliferation in the liver in rats after administration of 2-nitropropane (*Hasegawa et al., 1995 and Sai et al., 1998*).

Lung cancer:

Ingestion of green tea (2% of diet) decreased the number of lung tumors induced by 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) in mice (*Xu et al., 1992*). This result was confirmed by another experiment in which mice were subcutaneously injected with lung carcinoma cells (*Sazuka et al., 1995*).

Ingestion of green tea during DENA treatment decreased the number of lung tumors in mice at different dosages (*Cao et al., 1996*). These suggest a possible chemopreventive activity of green tea on lung tumors.

Gastrointestinal cancer:

Hamsters were treated with topical DMBA to induce oral tumors in the buccal pouch (*Li et al., 1999 and Chen et al., 2002*). Oral administration of green tea before and until the end of the experiment reduced the incidence of dysplasia and oral carcinoma.

N-ethyl-N-nitro-N-nitrosoguanidine (ENNG) and azoxymethane (AOM) cause intestinal or colorectal tumors after chronic administration. Green tea (0.1–2.0% of diet) decreased the number of duodenal or colon tumors induced by the various promoters (*Yamane et al., 1996*). In parallel, ingestion of epigallocatechin-3-gallate (EGCG) by rats decreased the incidence of gastric carcinogenesis induced by methyl-N-nitro-N-nitrosoguanidine (MNNG). These findings suggest that green tea catechins and EGCG are useful in preventing gastrointestinal carcinogenesis. Two important mechanisms of action of green tea may be inhibition of cancer cell proliferation and induction of apoptosis. After ingestion, green tea catechins are present as native forms in the digestive

tract. Because they are not completely absorbed by the gut (*Chen et al., 1997*), catechins can be present at high concentrations in the intestinal lumen and in this way can interact directly with duodenal or colon tumors by influencing apoptosis and proliferation.

Toxicity:

Green tea is generally considered a safe, non-toxic beverage and consumption is usually without side-effects. The average cup of green tea, however, contains from 10-50 mg of caffeine and overconsumption may cause irritability, insomnia, nervousness, and tachycardia. Because studies on its possible teratogenic effect are inconclusive, caffeine consumption is contraindicated during pregnancy. Lactating women should also limit caffeine intake to avoid sleep disorders in infants (*DerMarderosian, 1999*).

Dosage:

The dosage for green tea beverage varies, depending on the clinical situation and desired therapeutic effect. The phenolic content of green tea infusion is between 50-100 mg polyphenols per cup, depending on species, harvesting variables, and brewing methods (*Yamimoto et al., 1997*) with typical dosages ranging from 3 to 10 cups per day. Cancer preventative effects are usually associated with dosages in the higher end of the range. Green tea extracts containing 80% total polyphenols are dosed at an average of 500-1500 mg per day (*Imai et al., 1997*).

Atorvastatin

Chemistry:

Atorvastatin calcium is a synthetic stereo isomer of a pentasubstituted pyrrole. Unlike the previously introduced prodrugs, lovastatin and simvastatin, which are inactive till get metabolised, atorvastatin is an active compound (*Malinowski, 1998*). It is designed as (βR, δR)-2-(4-fluorophenyl)-β, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid (*Bakker-Arkema et al., 1997*).

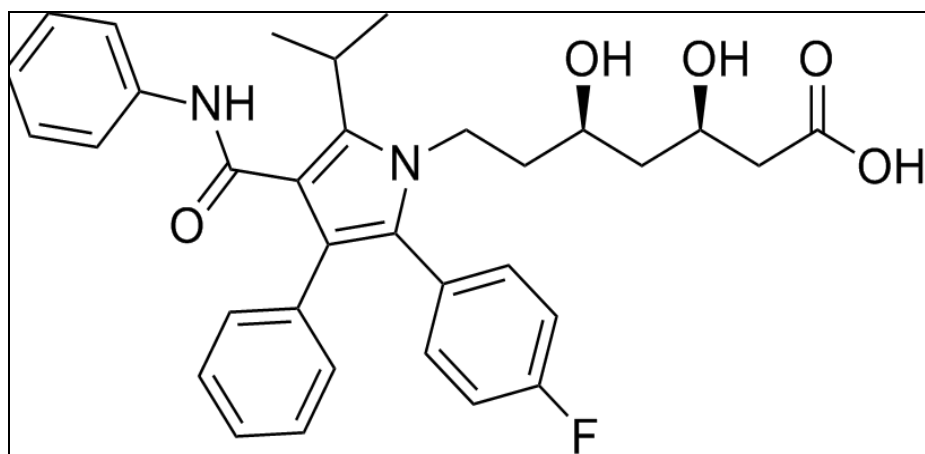


Figure (2) shows the chemical structure of atorvastatin (*Bakker-Arkema et al., 1997*).

Pharmacokinetics:

Atorvastatin is rapidly absorbed when given orally and peak plasma level occurs at nearly 2.5 hours. The absorption of atorvastatin is non-linear and dose dependent. Due to extensive first-pass metabolism, the bioavailability of atorvastatin is approximately 12% and is not significantly affected by food. It is about 98% bound to plasma proteins and metabolised extensively by CYP3A₄ to active metabolites, which

account for about 70% of the circulating HMG-CoA reductase inhibitory activity. Atorvastatin and its metabolites are eliminated primarily in bile following hepatic and/or extra-hepatic metabolism; however the drug does not appear to undergo enterohepatic re-circulation. Mean plasma elimination half-life is 14 hours, but because of active metabolites, the half-life of HMG-CoA reductase inhibitory activity is nearly 24 hrs (*Desager and Hormans, 1996*).

Pharmacodynamics:

Atorvastatin, like all statins, is a selective, competitive inhibitor of HMG-CoA reductase. HMG-CoA reductase catalyzes the rate limiting step in hepatic intracellular cholesterol synthesis. HMG-CoA reductase converts HMG-CoA to mevalonate in the cholesterol synthesis cascade (*Armstrong et al., 2005*). Inhibition of intrahepatocellular cholesterol synthesis results in the activation of sterol regulatory element binding proteins (SREBPs). SREBPs are transcription factors and are part of a cellular signaling cascade responsible for the regulation of LDL-R (LDL-receptor) gene expression. Once activated, SREBPs are able to diffuse across the nuclear membrane where they bind to sterol response elements (SREs) resulting in up-regulation of the LDL-R gene transcription and increased expression of LDL-R in the hepatocellular membrane. The increased expression of LDL-R causes increased cellular uptake of LDL molecules effectively lowering the intravascular (blood) circulating LDL concentration (*Armstrong et al., 2005*).

Atorvastatin has also been shown to elevate of nitrous oxide production. It was found to reduce the size of atherosclerotic lesion and decrease vascular smooth muscle cell proliferation in in-vitro model. These effects raise a hope that atorvastatin may promote platelet

deaggregation and vasodilatation in patients of dyslipidaemia (*Tannous et al., 1999*).

Indications:

Atorvastatin is indicated as an adjunct to diet for the treatment of Hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson types IIa and IIb) to reduce total cholesterol, LDL-C, apo-B, and TG levels, as well as increase HDL levels (*Andrews et al., 2001*).

Substantial data has recently accumulated showing that atorvastatin exert various effects on multiple targets, namely pleiotropic effects, including the improvement of vascular endothelial function, inhibition of vascular smooth muscle cell proliferation and migration, anti-inflammatory actions, anti-oxidative effects and stabilization of vulnerable plaques. These effects have potential in the treatment of coronary artery disease in various settings, such as prevention of its onset as well as its progression, or plaque rupture (*Inoue and Node, 2007*).

The molecular mechanisms underlying the effects of atorvastatin on endothelial function and oxidative stress in particular inhibition of small GTP-binding proteins seems to play an important role in mediating the pleiotropic effects of atorvastatin (*Lahera et al., 2007*)

Adverse effects:

Atorvastatin is generally well tolerated and adverse reactions have been mild and transient. Frequently encountered adverse effects are constipation, flatulence, dyspepsia and abdominal pain. Headache, rash and sleep disturbances have also been reported. Atorvastatin, like other HMG-CoA reductase inhibitors, have been associated with abnormal

liver function values. Persistent elevations ($>3 \times$ upper limit of normal value) in serum transaminases have been noticed in 0.7% of patients receiving atorvastatin. Hence, it is recommended that liver function tests should be performed before initiation of treatment and after 6 and 12 weeks of therapy. For patients on chronic therapy periodic (semi-annually) assessment of liver function is necessary. Patients who develop increased transaminase levels should be monitored until the abnormalities resolve (*Malinowski, 1998*).

Rhabdomyolysis with acute renal failure secondary to myoglobinuria has been reported with other drugs in this class but not so far with atorvastatin. Uncomplicated myalgia has been reported in atorvastatin-treated patients. Atorvastatin therapy should be discontinued if markedly elevated creatine phosphokinase (CPK) levels occur or myopathy is diagnosed or suspected. Although atorvastatin lacks teratogenicity in animal studies, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers (*Malinowski, 1998*).

Drug interactions:

Concurrent use of atorvastatin with drugs like erythromycin, azole antifungals (e.g. ketoconazole or fluconazole), cyclosporine, gemfibrozil, or niacin that may interfere with its metabolism or its protein binding may increase serum concentrations of atorvastatin and the risk of myopathy. Concurrent use of atorvastatin may increase digoxin serum concentrations (*Bakker-Arkema et al., 1997*). Grape fruit juice has been found to elevate bioavailability of atorvastatin probably by decreasing CYP3A₄-mediated first-pass metabolism of atorvastatin in the small intestine (*Lilja et al., 1999*).

Enalapril

Chemistry:

Enalapril maleate is an angiotensin converting enzyme (ACE) inhibitor. It is an analog of a tripeptide and a prodrug that is not highly active. It is designed as 1-[2-(1-ethoxycarbonyl-3-phenyl-propyl) aminopropanoyl] pyrrolidine-2-carboxylic acid. (*Dipette et al., 1985*).

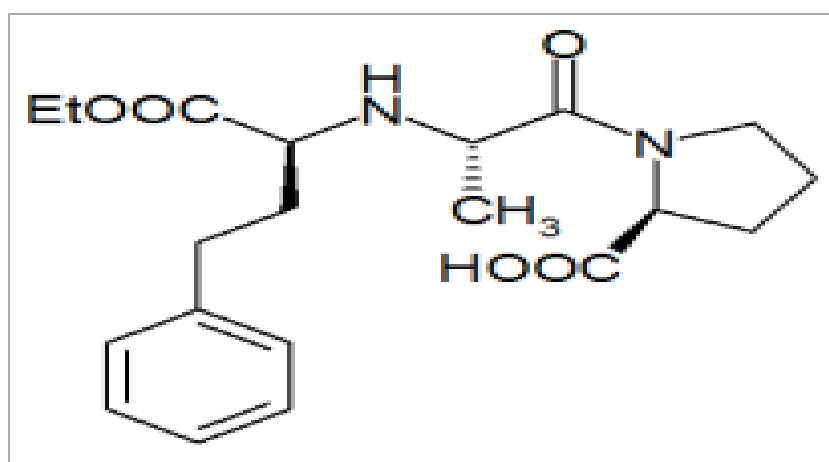


Figure (3) shows the chemical structure of enalapril (*Dipette et al., 1985*).

Pharmacokinetics:

Enalapril is a prodrug that is not highly active and, as such, it must be hydrolyzed by esterases in the liver to produce the active parent dicarboxylic acid, enalaprilat. Enalapril is rapidly absorbed when given orally and has an oral bioavailability of about 60% (not reduced by food). Although, peak concentrations in plasma occur within an hour, enalaprilat concentrations do not peak until 3 to 4 hours. Enalapril has a half-life of only 1.3 hours. However, enalaprilat, because of tight binding to ACE, has a plasma half-life of about 11 hours. Nearly all the drug is

eliminated by the kidneys either as intact enalapril or enalaprilat (*Jackson, 2001*).

Pharmacodynamics:

the renin-angiotensin system plays a major role in maintaining a constant set point for long-term levels of arterial blood pressure despite extreme changes in dietary Na⁺ intake (*Hall et al., 1980*).

The essential effect of enalapril on the renin-angiotensin system is to inhibit the conversion of the relatively inactive angiotensin I to the active angiotensin II. Thus, enalapril attenuates or abolishes responses to angiotensin I but not to angiotensin II. In this regard, the principal pharmacological and clinical effects of enalapril seems to arise from suppression of synthesis of angiotensin II. Nevertheless, ACE is an enzyme with many substrates, and inhibition of ACE therefore may induce effects unrelated to reducing the levels of angiotensin II. Since enalapril increases bradykinin levels, and since bradykinin stimulates prostaglandin biosynthesis, bradykinin and/or prostaglandins may contribute to the pharmacological effects of enalapril. Since the metabolism of angiotensin I to angiotensin II is blocked by enalapril, angiotensin I is directed down alternative metabolic routes resulting in the increased production of peptides such as angiotensin (*Davie et al., 1999*).

Indications:

Hypertension: Enalapril alone normalize blood pressure in approximately 50% of patients with mild-to-moderate hypertension, and many consider enalapril and other ACE inhibitors first-line drugs for the treatment of high blood pressure, except for elderly African-American patients. Ninety percent of patients with mild-to-moderate hypertension

will be controlled by the combination of an ACE inhibitor with either a Ca^{2+} channel blocker, β -adrenergic receptor blocker, or diuretic (*Zusman, 1993*).

Myocardial Infarction. The use of enalapril in myocardial infarction is rapidly evolving. Several large, prospective, randomized clinical studies (*Cohn et al., 1991 and SOLVD, 1991 and 1992*) provide convincing evidence that ACE inhibitors reduce overall mortality when treatment is begun during the periinfarction period. In this regard, clinical trials with ACE inhibitors in myocardial infarction can be divided into two groups: (1) treatment for several years of postmyocardial infarction patients with left ventricular systolic dysfunction (with or without overt heart failure); and (2) treatment for several weeks of postmyocardial infarction patients regardless of ventricular function. These studies suggest that, in selected high-risk patients (i.e., those with systolic dysfunction), ACE inhibitors save 40 to 70 lives per 1000 patients. Short-term treatment of unselected postmyocardial infarction patients saves about 5 lives per 1000 (*Pfeffer, 1995*).

Progressive Renal Impairment: The combination of diabetes mellitus and hypertension leads to diabetic nephropathy and is the major cause of end-stage renal failure. Enalapril has been shown in numerous animal studies (*Hoelscher et al., 1995*) and in several small clinical trials (*Keilani et al., 1995*) to retard significantly the loss of kidney function associated with diabetic nephropathy.

Adverse effects:

Metabolic side effects: They are not encountered during long-term therapy with enalapril. The drug does not alter plasma concentrations of uric acid or Ca^{2+} (*Frohlich, 1989*) and may actually improve insulin sensitivity in patients with insulin resistance and decrease cholesterol levels and lipoprotein(a) levels in proteinuric renal disease (*Keilani et al., 1995*). Serious untoward reactions to enalapril are rare (*Materson, 1992*), and in general enalapril is well tolerated.

Cough. In 5% to 20% of patients, enalapril induces dry cough; it is usually not dose related, occurs more frequently in women than in men, usually develops between 1 week and 6 months after initiation of therapy, and sometimes requires cessation of therapy. This adverse effect may be mediated by the accumulation in the lungs of bradykinin, substance P, and/or prostaglandins. Once enalapril is stopped, the cough disappears, usually within 4 days (*Israili and Hall, 1992*).

Fetopathic Potential: Although enalapril is not teratogenic during the early period of organogenesis (first trimester), continued administration of it during the second and third trimesters can cause oligohydramnios, fetal calvarial hypoplasia, fetal pulmonary hypoplasia, fetal growth retardation, fetal death, neonatal anuria, and neonatal death. (*Brent and Beckman, 1991*).

Drug Interactions:

Antacids may reduce the bioavailability of ACE inhibitors, NSAIDs may reduce the antihypertensive response to ACE inhibitors, and K^{+} -sparing diuretics and K^{+} supplements may exacerbate ACE

inhibitor-induced hyperkalemia. ACE inhibitors may increase plasma levels of digoxin and lithium and may increase hypersensitivity reactions to allopurinol (*Guazzi et al., 1998*).