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Effect of Inhaled Corticosteroids and Exposure to Tobacco Smoke on Bone Mineral Density In Children

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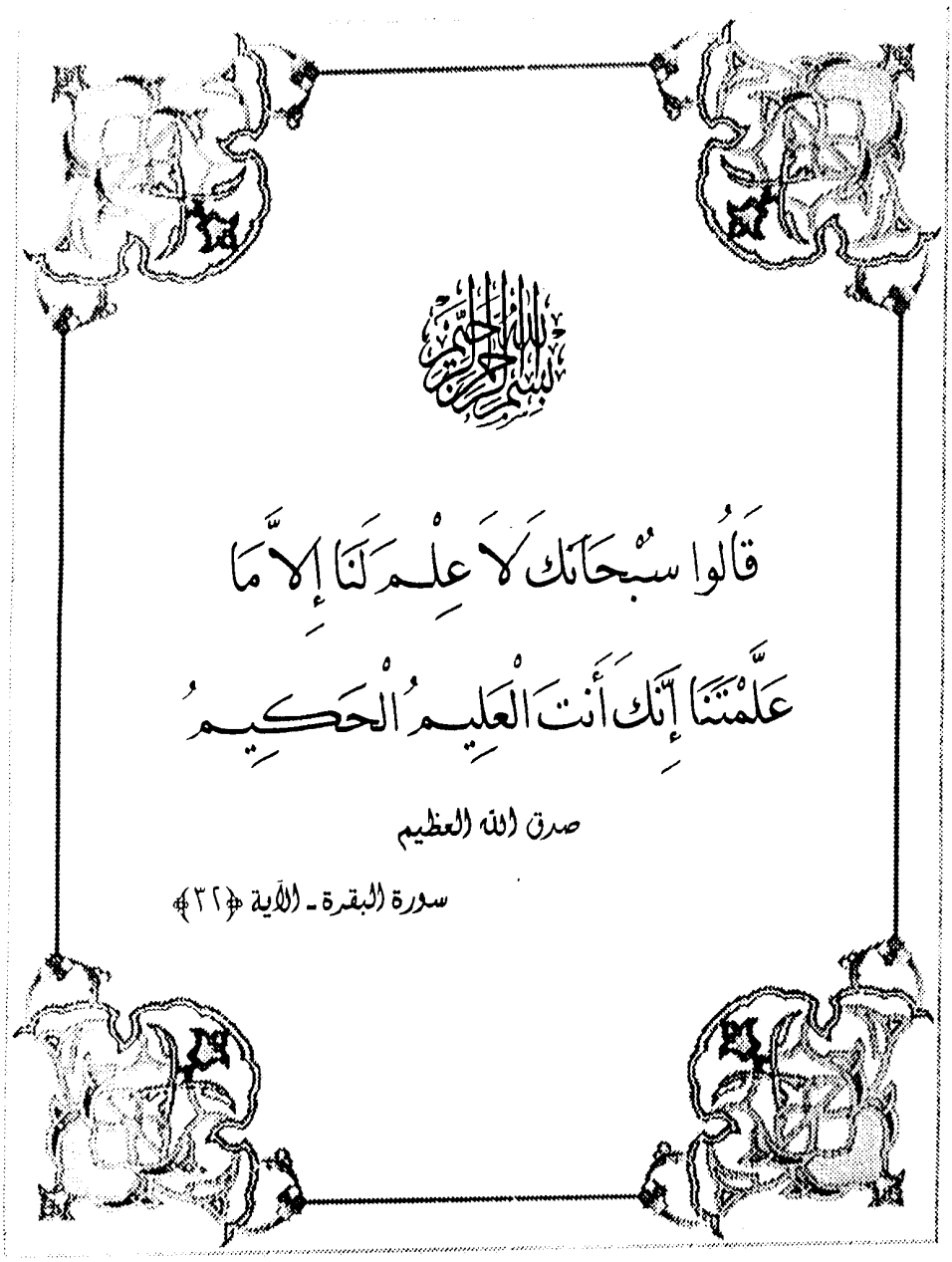

To MY

GREAT PARENTS

And MY

BELOVED SON,

GOD bless them all

ACKNOWLEDGMENT

In the name of ALLAH, the first, the foremost and the greatest of all.

I kneel to express the utmost gratitude, of one of **His** unlimited blessings throughout my life, for helping me to fulfill this work.

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CHAPTER III : ENVIRONMENTAL TOBACCO SMOKE

LIST of ABBREVIATIONS

BDP	: Beclomethasone dipropionate
BMC	: Bone mineral content
a BMD	: Areal bone mineral density
BMD	: Bone mineral density
BMI	: Body mass index
BUD	: Budesonide
CDGP	: Constitutional Delay of Growth and Puberty
COPD	: Chronic obstructive pulmonary disease
CR	: Chemical Regimen
DALYs	: Disability-adjusted life years
DM	: Diabetes Mellitus
DEXA/DXA	: Dual energy *x* ray absorptiometry
ELISA	: Enzyme Linked Immunosorbant Assay
ETS	: Environmental tobacco smoke
EX-induced	: Exercise-induced
FEV1	: Forced expiratory volume in 1 second
FP	: Fluticasone propionate
FVC	: Forced vital capacity
GC/MS	: Gas chromatography/ Mass spectrometry
HPA	: Hypothalamic-pituitary-adrenal axis
ICS	: Inhaled corticosteroids
IGF-1	: Insulin-like growth factor 1
IJO	: Idiopathic juvenile osteoporosis
IQ	: Intelligent Questiont
JRA	: Juvenile rheumatoid arthritis
MRI	: Magnetic resonance imaging

LIST of ABBREVIATIONS

MS	: Mainstream smoke
OI	: Osteogenesis imperfecta
P.C.	: Personal computer
PBM	: Peak bone mass
PEF	: Peak expiratory flow
PHV	: Peak height velocity
QCT	: Quantitative computed tomography
RDA	: Recommended daily allowance
RSV	: Respiratory syncytial virus
SDs	: Standard deviations
SIDS	: Sudden infant death syndrome
SS	: Sidestream tobacco smoke
Th2	: T helper 2 lymphocytes
TLR2	: Toll-like receptor 2
UVB	: Ultra violet B
VEGF	: Vascular endothelial growth factor
VOCs	: Volatile organic compounds

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Review of Literature, Subjects and Methods:

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Introduction

Introduction

Osteoporosis literally means "porous bone", it usually affects people later in life but it may affect children and adolescents. When it occurs, it could be due to; primary disorders as juvenile arthritis, DM or thyroid dysfunction or secondary to medications as corticosteroids and anti-convulsants or behaviors as prolonged inactivity, inadequate nutrition or smoking, this is called secondary osteoporosis ***(Khosla and Melton 1995).***

It may also be the result of a genetic disorder such as osteogenesis imperfecta. Sometimes there is no identifiable cause of juvenile osteoporosis, this is known as idiopathic juvenile osteoporosis ***(Norman 1996 & Dent and Friedman 1965).***

Asthma is a problem worldwide, with an estimated 300 million affected individuals ***(Masoli et al., 2004 & Beasley 2004).*** The World Health Organization has estimated that 15 million disability-adjusted life years (DALYs) are lost annually due to asthma, representing 1% of the total global disease burden ***(Masoli et al., 2004).***

Inhaled glucocorticosteroids are the most effective controller therapy for asthma in children of all ages. Corticosteroid may affect bone metabolism through direct effect on osteoblasts, decreasing bone formation, lowering of sex hormone production, increasing bone resorption and direct antagonism of intestinal calcium absorption ***(GINA 2006)***.

Environmental tobacco smoke (ETS) is the smoke present in the air that nonsmokers inhale, it has recently been classified as class I carcinogen by the International Agency for Research on Cancer ***(IARC 2004).***

A large literature links both prenatal maternal smoking and children's ETS exposure to decreased lung growth and increased rates of respiratory tract infections, otitis media, and childhood asthma, with the severity of these problems increasing with increased exposure ***(DiFranza et al., 2004).***

AIM OF STUDY

Aim of Work

The aim of this study;

1) To detect the effect of Inhaled corticosteroids on bone mineral density of asthmatic children.

2) To detect the effect of exposure to environmental tobacco smoke on bone mineral density of healthy exposed children.

3) To detect the combined effect of both inhaled corticosteroids and exposure to environmental tobacco smoke on bone mineral density of asthmatic children.

Literature Review

CHAPTER I

BRONCHIAL ASTHMA

DEFINITION:

Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread, but variable, airflow obstruction within the lung that is often reversible either spontaneously or with treatment ***(GINA 2006).***

There is now good evidence that the clinical manifestations of asthma symptoms, sleep disturbances, limitations of daily activity, impairment of lung function, and use of rescue medications, can be controlled with appropriate treatment. When asthma is controlled, there should be no more than occasional recurrence of symptoms and severe exacerbations should be rare ***(Vincent et al., 2006).***

PREVALENCE:

Asthma is a problem worldwide, with an estimated 300 million affected individuals. Despite hundreds of reports on the prevalence of asthma in widely differing populations, the lack of a precise and universally accepted definition of asthma makes reliable comparison of reported prevalence from different parts of the world problematic ***(Masoli et al., 2004 & Beasley 2004)***.

Nonetheless, based on the application of standardized methods to measure the prevalence of asthma and wheezing illness in children ***(Beasley 2004)*** and adults ***(Yan et al., 2005)***, it appears that the global prevalence of asthma ranges from 1% to 18% of the population in different countries ***(Masoli et al., 2004 & Beasley 2004)***.

There is good evidence that asthma prevalence has been increasing in some countries ***(Carvajal-Uruena et al., 2005, Ko et al., 2005 &Yan et al., 2005)*** and has recently increased but now may have stabilized in others ***(Teeratakulpisarn et al., 2004 & Garcia-Marcos et al., 2004).***

In Egypt, 23.2% of wheezy infants were proved to be real asthmatics. Asthma prevalence among school children aged 5-15 years was found to be 8.2%, half of which are graded as moderate and severe ***(El Lawindi et al., 2003& El Hefney et al., 1999)***.

Palestinian children have asthma symptoms rates that are similar to several countries in the Mediterranean region such as Spain and Turkey, but still lower than other Middle East countries such as Saudi Arabia and Israel ***(El Sharif et al., 2003).***

The World Health Organization has estimated that 15 million disability-adjusted life years (DALYs) are lost annually due to asthma, representing 1% of the total global disease burden ***(Masoli et al., 2004).***

PATHOPHYSIOLOGY:

Asthma is an inflammatory disorder of the airways, which involves several inflammatory cells and multiple mediators that result in characteristic pathophysiological changes ***(Tattersfield et al., 2002 & Busse and Lemanske 2001).***

The airway inflammation in asthma is persistent even though symptoms are episodic, and the relationship between the severity of asthma and the intensity of inflammation is not clearly established ***(Cohn et al 2004 & Bousquet et al., 2000).***

The inflammation affects all airways including in most patients the upper respiratory tract and nose but its physiological effects are most pronounced in medium-sized bronchi ***(GINA 2006)***.

A-Inflammatory cells:

There are increased numbers of activated mast cells, activated eosinophils, dendritic cells, macrophages and neutrophils ***(Wenzel 2003).***

Increased numbers of T cell receptors in variant natural killer T cells and T helper 2 lymphocytes (Th2), which release mediators that contribute to symptoms ***(Akbari et al., 2006).***

Structural cells of the airways - airway epithelial cells, airway smooth muscle cells, endothelial cells, fibroblasts and myofibroblasts and airway nerves - also produce inflammatory mediators, and contribute to the persistence of inflammation in various ways ***(Groneberg et al., 2004)***.

B-Inflammatory mediators:

Over 100 different mediators, chemokines, cysteinyl leukotrienes, cytokines, histamine, nitric oxide and prostaglandin D2, are now recognized to be involved in asthma and mediate the complex inflammatory response in the airways ***(Barnes et al., 1998).***

C- Structural changes in the airways:

There are characteristic structural changes, often described as airway remodeling, in the airways of asthma patients. Some of these changes are related to the severity of the disease and may result in relatively irreversible narrowing of the airways ***(James 2005 & Vignola et al., 2003).*** Airway smooth muscle increases, due to hypertrophy " increased size of individual cells" and hyperplasia " increased cell division", blood vessels in airway walls proliferate under the influence of growth factors such as vascular endothelial growth factor (VEGF) and mucus hypersecretion results from increased numbers of goblet cells in the airway epithelium and increased size of submucosal glands ***(Hirst et al., 2004)***.

D- Airway Narrowing in Asthma:

It is the final common pathway leading to symptoms and physiological changes in asthma. Several factors contribute to the development of airway narrowing in asthma;

- **Airway smooth muscle** contraction in response to multiple bronchoconstrictor mediators and neurotransmitters is the predominant mechanism of airway narrowing and is largely reversed by bronchodilators.
- **Airway edema** is due to increased microvascular leakage in response to inflammatory mediators. This may be particularly important during acute exacerbations.

- **Airway thickening** due to structural changes, often termed "remodeling," may be important in more severe disease and is not fully reversible by current therapy.
- **Mucus hypersecretion** may lead to luminal occlusion ("mucus plugging") and is a product of increased mucus secretion and inflammatory exudates ***(GINA guidelines 2006).***

FACTORS INFLUENCING THE DEVELOPMENT AND EXPRESSION OF ASTHMA:

Factors that influence the risk of asthma can be divided into those that cause the development of asthma (which are primarily genetic) and those that trigger asthma symptoms (which are usually environmental factors); some factors do both ***(Busse and Lemanske 2001).***

Genes likely interact both with other genes and with environmental factors to determine asthma susceptibility. In addition, developmental aspects, such as the maturation of the immune response and the timing of infectious exposures during the first years of life, are emerging as important factors modifying the risk of asthma in the genetically susceptible person ***(Ober 2005 & Holgate 1999).***

The apparent racial and ethnic differences in the prevalence of asthma reflect underlying genetic variances with a significant overlay of socioeconomic

and environmental factors. Much of what is known about asthma risk factors comes from studies of young children. Risk factors for the development of asthma in adults, particularly de novo in adults who did not have asthma in childhood, are less well defined ***(GINA 2006)***.

I – Host Factors:

1- *Genetic:*

Asthma has a heritable component, but it is not simple. Current data show that multiple genes may be involved in the pathogenesis of asthma, and different genes may be involved in different ethnic groups ***(Holloway et al., 1999 & Wiesch et al., 1999)***.

The search for genes linked to the development of asthma has focused on four major areas: production of allergen specific IgE antibodies (atopy); expression of airway hyperresponsiveness; generation of inflammatory mediators, such as cytokines, chemokines, and growth factors; and determination of the ratio between Th1 and Th2 immune responses (as relevant to the hygiene hypothesis of asthma) ***(Strachan 1989).***

There is evidence that gene-environment interactions play an especially important role in diseases, such as asthma, that have a great deal of variability in their clinical expression. Environmental factors can modify the clinical expression

of genetic variability in a variety of patterns. In fact, certain genetic polymorphisms can increase, reduce, or have no effect on the clinical expression of asthma ***(Martinez 2004).***

There is a strong relationship between exposure to endotoxin and protection from asthma, strongly suggesting that innate immune responses are responsible. A specific polymorphism of Toll-like receptor 2 (TLR2) is associated with protection from asthma among children in farming families, with high exposure to microbial products, but not among families living in relatively "clean" urban and suburban homes. The polymorphism of the CD14 gene (CD14/-159), which is also involved in immune recognition of microbial products, such as endotoxin, has distinct associations with serum-IgE levels depending on the degree of exposure to animals; no effect in the absence of animals and opposite effects in children exposed to dogs and cats (TT associated with reduced IgE) vs children exposed to farm animals (TT associated with higher IgE). Presumably, the different levels of endotoxin in these environments modified the nature of the relationships between CD14 genotype and IgE levels, and the mechanism for this effect is under investigation ***(Eder et al., 2004).***

In addition to genes that predispose to asthma there are genes that are associated with the response to asthma treatments. For example, variations in the gene encoding the beta-adrenoreceptor have been linked to differences in subjects' responses to β2-agonists ***(Israel et al., 2004).*** Other genes of interest modify the

responsiveness to glucocorticosteroids ***(Ito et al., 2006)*** and leukotriene modifiers ***(In et al., 1997).***

Studies have sequenced the promoter regions of the 5-lipoxygenase and leukotriene C4 (LTC4) genes that regulate leukotriene biosynthesis. SNP A (-444) C) has been identified that appears to regulate leukotriene production ***(Holgate 2004).*** This polymorphism appears to increase the risk of aspirin-sensitive bronchospasm and is overrepresented in moderate-to-severe asthma. Recently, there is evidence that this SNP also correlates with the response to pranlukast, a leukotriene-receptor antagonist. The results of this work suggest that if additional genotype/therapeutic response relationships can be distinguished, clinicians may eventually be able to screen key genetic regions in blood samples from asthmatics to develop a profile that would be useful in predicting the best combination of asthma controllers, while minimizing the risk of side effects ***(Israel et al., 2004, Tattersfield and Hall 2004 & Drazen and Weiss 2002).***

2- *Sex:*

Male sex is a risk factor for asthma in children. Prior to the age of 14, the prevalence of asthma is nearly twice as great in boys as in girls ***(Horwood et al., 1985)***. As children get older the difference between the sexes narrows, and by adulthood the prevalence of asthma is greater in women than in men.

The reasons for this sex-related difference are not clear. However, lung size is smaller in males than in females at birth but larger in adulthood ***(Martinez et al., 1995)***.

3- *Obesity*:

Obesity has also been shown to be a risk factor for asthma, a study done in year 2006 concluded that asthma was found to occur more frequently in girls with overweight or obesity ***(Ostrowska-Nawaycz et al., 2006)***, however another study done in 2004 suggested that there is no association between asthma and obesity among Canadian children ***(To et al., 2004)*** .

Repeated cross sectional studies in the same population are needed to answer the question ***(Chinn and Rona 2005)***.

Certain mediators such as leptins may affect airway function and increase the likelihood of asthma development ***(Beuther et al., 2006 & Shore and Fredberg 2005),*** leptin levels was found to be higher in asthmatic patients ***(Gurkan et al., 2004).***

A possible relationship has been debated between leptin levels and obesity related respiratory disorders (obesity sleep apnea syndrome and obesity hypoventilation syndrome) ***(Ulukavak et al., 2005)***.

II - Environmental Factors:

1. *Allergens:*

Although indoor and outdoor allergens are well known to cause asthma exacerbations, their specific role in the development of asthma is still not fully resolved. Birth-cohort studies have shown that sensitization to house dust mite allergens, cat dander, dog dander ***(Wahn et al., 1997 & Sporik et al., 1990)***, and Aspergillus mold are independent risk factors for asthma like symptoms in children up to 3 years of age ***(Hogaboam et al., 2005)***.

The relationship between allergen exposure and sensitization in children is not straightforward. It depends on the allergen, the dose, the time of exposure, the child's age, and probably genetics as well. For some allergens, such as those derived from house dust mites and cockroaches, the prevalence of sensitization appears to be directly correlated with exposure ***(Huss et al., 2001& Wahn et al., 1997)***.

In the case of dogs and cats, some epidemiologic studies have found that early exposure to these animals may protect a child against allergic sensitization or the development of asthma ***(Gern et al., 2004, Ownby et al., 2002 & Platts-Mills et al., 2001)***, but others suggest that such exposure may increase the risk of allergic sensitization ***(Almqvist et al., 2003, Ownby et al., 2002, Celedon et al., 2002 & Melen et al., 2001)***.

The prevalence of asthma is reduced in children raised in a rural setting, which may be linked to the presence of endotoxin in these environments ***(Braun-Fahrlander 2003).***

2. *Infections:*

During infancy, a number of viruses have been associated with the inception of the asthmatic phenotype. Respiratory syncytial virus (RSV) and parainfluenza virus produce a pattern of symptoms including bronchiolitis that parallel many features of childhood asthma ***(Gern and Busse 2002 & Sigurs et al., 2000).***

The "hygiene hypothesis" of asthma suggests that exposure to infections early in life influences the development of a child's immune system along a "nonallergic" pathway, leading to a reduced risk of asthma and other allergic diseases. Although the hygiene hypothesis continues to be investigated, this mechanism may explain observed associations between family size, birth order, day-care attendance, and the risk of asthma.

For example, young children with older siblings and those who attend day care are at increased risk of infections, but enjoy protection against the development of allergic diseases, including asthma later in life ***(de Meer et al., 2005, Illi et al., 2001 & Ball et al., 2000).***

The interaction between atopy and viral infections appears to be a complex relationship, in which the atopic state can influence the lower airway

response to viral infections, viral infections can then influence the development of allergic sensitization, and interactions can occur when individuals are exposed simultaneously to both allergens and viruses ***(Zambrano et al., 2003)***.

3. *Tobacco smoke:*

Tobacco smoking is associated with accelerated decline of lung function in people with asthma, increases asthma severity, may render patients less responsive to treatment with inhaled ***(Chalmers et al., 2002)*** and systemic ***(Chaudhuri et al., 2003)*** glucocorticosteroids, and reduces the likelihood of asthma being controlled ***(Bateman et al., 2004).***

Exposure to tobacco smoke both prenatally and after birth is associated with measurable harmful effects including a greater risk of developing asthma-like symptoms in early childhood. Distinguishing the independent contributions of prenatal and postnatal maternal smoking is problematic ***(Kulig et al., 1999).***

Exposure to environmental tobacco smoke (passive smoking) increases the risk of lower respiratory tract illnesses in infancy ***(Nafstad et al., 1997)*** and childhood ***(American Academy of Pediatrics 1997).*** Passively smoking children had subclinical bronchial hyperreactivity with various grades, and some of them may turn to be asthmatics. Pulmonary function of the passive smokers depend on multifactors in particular, number of smoked cigarette and duration of exposure

to tobacco smoke. Health education program to explain the hazards effect of smoke to both active smoker and passive smokers are highly recommended. Also, routine examination of passive smokers by metacholine challenge test (MCT) at regular intervals to detect asthmatic patients as early as possible ***(Deraz et al., 2001).***

Studies of lung function immediately after birth have shown that maternal smoking during pregnancy has an influence on lung development ***(Martinez et al., 1995).*** Infants of smoking mothers are 4 times more likely to develop wheezing illnesses in the first year of life ***(Dezateux et al., 1999).*** There is little evidence (based on meta-analysis) that maternal smoking during pregnancy has an effect on allergic sensitization ***(Strachan and Cook 1998).***

4. *Outdoor/indoor air pollution:*

Children raised in a polluted environment have diminished lung function ***(Gauderman et al., 2004)***, but the relationship of this loss of function to the development of asthma is not known ***(American Thoracic Society 2000).***

High degree of air pollution has deleterious and adverse effects on pulmonary functions in school children with both restrictive and obstructive abnormalities with increase incidence of recurrent respiratory tract infections ***(Deraz et al., 2001).***

Outbreaks of asthma exacerbations have been shown to occur in relationship to increased levels of air pollution, which may be related to a general increase in the level of pollutants or to specific allergens to which individuals are sensitized, yet the role of pollutants in the development of asthma is less well defined. Similar associations have been observed in relation to indoor pollutants, e.g., smoke and fumes from gas and biomass fuels used for heating and cooling, molds, and cockroach infestations ***(Chen et al., 2004, Marks et al., 2001& Anto et al., 1999)***.

5. *Diet:*

The role of diet, particularly breast-feeding, in relation to the development of asthma has been extensively studied and, in general, the data reveal that infants fed formulas of intact cow's milk or soy protein have a higher incidence of wheezing illnesses in early childhood compared with those fed breast milk ***(Friedman and Zeiger 2005).***

Breast-feeding might delay the onset of or actively protect children < 24 months of age against asthma and recurrent wheeze and might reduce the prevalence of asthma and wheeze among children exposed to ETS ***(Jones and Jones 2004 & Chalada et al., 2003).***

Some data also suggest that certain characteristics of Western diets, such as increased use of processed foods and decreased antioxidant (in the form of fruits and vegetables), increased n-6 polyunsaturated fatty acid (found in margarine and vegetable oil), and decreased n-3 polyunsaturated fatty acid (found in oily fish) intakes have contributed to the recent increases in asthma and atopic disease ***(Devereux and Seaton 2005).***

Dietary supplementation with probiotics given prenatally to mother and postnatally for six months to their infants resulted in 50% reduction in the rate of atopic eczema at the age of 2 years ***(Halken 2004 & Furrie 2005).***

Early vitamin supplementation is associated with increased risk of asthma in black chikdren and food allergies in exclusively formula fed children ***(Ahn et al., 2005).***

DIAGNOSIS:

Diagnosis in patients with suspected asthma differs among different age groups: infants, children, young adults, and the elderly.

I - Children 5 years and Younger:

Episodic wheezing and cough is very common even in children who do not have asthma and particularly in those under age 3 ***(Wilson 1989).*** Three categories of wheezing have been described in children 5 years and younger:

- *Transient early wheezing*, which is often outgrown in the first 3 years. This is often associated with prematurity and parental smoking.
- *Persistent early-onset wheezing* (before age 3), these children typically have recurrent episodes of wheezing associated with acute viral respiratory infections, have no evidence of atopy ***(Martinez 2003)*** and, unlike children in the next category of late onset wheezing/asthma, have no family history of atopy. The symptoms normally persist through school age and are still present at age 12 in a large proportion of children. The cause of the episode is usually the respiratory syncytial virus in children younger than age 2, while other viruses predominate in older preschool children.
- *Late-onset wheezing/asthma*, these children have asthma which often persists throughout childhood and into adult life ***(Sears 2003 & Castro-Rodriguez 2000)***. They typically have an atopic background, often with eczema, and airway pathology is characteristic of asthma.

The following categories of symptoms are highly suggestive of a diagnosis of asthma: ***(GINA 2006)***

- Frequent episodes of wheeze (more than once a month).

- Activity-induced cough or wheeze.

- Nocturnal cough in periods without viral infections.

- Absence of seasonal variation in wheeze and symptoms that persist after age 3.

- A simple clinical index based on the presence of a wheeze before the age of 3, and the presence of one major risk factor (parental history of asthma or eczema) or

two of three minor risk factors (eosinophilia, wheezing without colds, and allergic rhinitis) has been shown to predict the presence of asthma in later childhood ***(Castro-Rodriguez 2000).***

A useful method for confirming the diagnosis of asthma in children 5 years and younger is a trial of treatment with short-acting bronchodilators and inhaled glucocorticosteroids. Marked clinical improvement during the treatment and deterioration when treatment is stopped supports a diagnosis of asthma. However, treating children at risk with inhaled glucocorticosteroids has not been shown to affect the development of asthma ***(Guilbert 2006).***

Children 4 to 5 years old can be taught to use a PEF meter, but to ensure reliability parental supervision is required ***(Sly 1994).***

Differential diagnosis of recurrent wheezing in children 5 years and younger :

- Chronic rhino-sinusitis.
- Gastroesophageal reflux.
- Recurrent viral lower respiratory tract infections.
- Cystic fibrosis.
- Bronchopulmonary dysplasia.
- Tuberculosis.
- Congenital malformation causing narrowing of the intrathoracic airways
- Foreign body aspiration.

• Primary ciliary dyskinesia syndrome.

• Immune deficiency.

• Congenital heart disease.

• Neonatal onset of symptoms (associated with failure to thrive), vomiting-associated symptoms, or focal lung or cardiovascular signs suggest an alternative diagnosis and indicate the need for further investigations. ***(GINA 2006)***

II - Older Children and Adults:

Asthma symptoms may be intermittent and non-specific, they may result in misdiagnosis, this is particularly true among children, where misdiagnoses include various forms of bronchitis or croup, and lead to inappropriate treatment. Diagnosis should be based on:

1- Medical History:

Symptoms such as episodic breathlessness, wheezing, cough, and chest tightness. Episodic symptoms after an incidental allergen exposure, seasonal variability of symptoms and a positive family history of asthma and atopic disease are also helpful diagnostic guides. Asthma associated with rhinitis may occur intermittently, with the patient being entirely asymptomatic between seasons or it may involve seasonal worsening of asthma symptoms or a background of persistent asthma ***(Levy et al., 2006)***.

Patients with cough-variant asthma ***(Corrao et al., 1979)*** have chronic cough as their principal, if not only, symptom. It is particularly common in children, and is often more problematic at night; evaluations during the day can be normal. For these patients, documentation of variability in lung function or of airway hyperresponsiveness, and possibly a search for sputum eosinophils, are particularly important ***(Gibson et al., 2002).*** Cough-variant asthma must be distinguished from so-called eosinophilic bronchitis in which patients have cough and sputum eoinophils but normal indices of lung function when assessed by spirometry and airway hyperresponsiveness ***(Gibson et al., 1989).***

Exercise-induced bronchoconstriction, physical activity is an important cause of asthma symptoms for most asthma patients, and for some it is the only cause. It typically develops within 5-10 minutes after completing exercise (it rarely occurs during exercise). Patients experience typical asthma symptoms, or sometimes a troublesome cough, which resolve spontaneously within 30-45 minutes. Some forms of exercise, such as running, are more potent triggers ***(Randolph 1997).*** It may occur in any climatic condition, but it is more common when the patient is breathing dry, cold air and less common in hot, humid climates ***(Tan et al., 1985).***

Rapid improvement of post-exertional symptoms after inhaled β2-agonist use, or their prevention by pretreatment with an inhaled β2-agonist

before exercise, supports a diagnosis of asthma. Some children with asthma present only with exercise-induced symptoms. In this group, or when there is doubt about the diagnosis, exercise testing is helpful. An 8-minute running protocol is easily performed in clinical practice and can establish a firm diagnosis of asthma ***(Anderson 2002).***

2 - Physical Examination:

The physical examination of the respiratory system may be normal. The most usual abnormal physical finding is wheezing on auscultation, however, wheezing may be absent or only detected when the person exhales forcibly, even in the presence of significant airflow limitation. Occasionally, in severe asthma exacerbations, wheezing may be absent owing to severely reduced airflow and ventilation. However, other physical signs reflecting the exacerbation and its severity, such as cyanosis, drowsiness, difficulty speaking, tachycardia, hyperinflated chest, use of accessory muscles, and intercostal recession may be present ***(GINA 2006)***.

3- Measurements of lung function:

Measurements of lung function, and particularly the demonstration of reversibility of lung function abnormalities, greatly enhance diagnostic confidence. This is because patients with asthma frequently have poor recognition of their symptoms and poor perception of symptom severity, especially if their

asthma is long-standing. It provides an assessment of the severity of airflow limitation, its reversibility and its variability ***(Killian et al., 2000)***.

► Reversibility is generally applied to rapid improvements in FEV1 (or PEF), measured within minutes after inhalation of a rapid-acting bronchodilator—for example after 200-400 mg salbutamol (albuterol)—or more sustained improvement over days or weeks after the introduction of effective controller treatment such as inhaled glucocorticosteroids ***(Pellegrino et al., 2005)*** .

► Variability refers to improvement or deterioration in symptoms and lung function occurring over time. It may be experienced over the course of one day (diurnal variability), from day to day, from month to month, or seasonally. History of variability is an essential component of both diagnosis and assessment of asthma control ***(GINA 2006)***.

Two methods have gained widespread acceptance for use in patients over 5 years of age. These are ***spirometry***, particularly the measurement of forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC), and ***peak expiratory flow (PEF) measurement.*** Predicted values of FEV1, FVC, and PEF based on age, sex, and height have been obtained from population studies. These are being continually revised, and with the exception of PEF for which the range of predicted values is too wide, they are useful for judging whether a given value is abnormal or not ***(GINA 2006).***

4 - Measurement of airway responsiveness:

For patients with symptoms consistent with asthma, but normal lung function, measurements of airway responsiveness to methacholine, histamine, mannitol, or exercise challenge may help to establish a diagnosis of asthma ***(Cockcroft 2003).***

Measurements of airway responsiveness reflect the "sensitivity" of the airways to factors that can cause asthma symptoms, but have limited specificity ***(Cockcroft et al., 1992).*** This means that a negative test can be useful to exclude a diagnosis of persistent asthma in a patient who is not taking inhaled glucocorticosteroid treatment, but a positive test does not always mean that a patient has asthma ***(Boulet 2003).*** This is because airway hyperresponsiveness has been described in patients with allergic rhinitis ***(Ramsdale et al., 1985)*** and in those with airflow limitation caused by conditions other than asthma, such as cystic fibrosis ***(van Haren et al., 1995),*** bronchiectasis, and chronic obstructive pulmonary disease (COPD) ***(Ramsdale et al., 1984).***

5 - Non-invasive markers of airway inflammation:

Evaluation of airway inflammation associated with asthma may be undertaken by examining spontaneously produced or hypertonic saline-induced sputum for eosinophilic or neutrophilic inflammation ***(Pizzichini et al., 1996)*** or measuring levels of exhaled nitric oxide (FeNO) ***(Kharitonov et al., 1997)*** and carbon monoxide (FeCO) ***(Horvath and Barnes 1999).***

6 - Measurements of allergic status:

Deliberate provocation of the airways with a suspected allergen or sensitizing agent may be helpful in the occupational setting, but is not routinely recommended, because it is rarely useful in establishing a diagnosis, requires considerable expertise and can result in life-threatening bronchospasm ***(Hoeppner et al., 1985).***

Differential diagnosis in older children and adults:

- Hyperventilation syndrome and panic attacks.
- Upper airway obstruction and inhaled foreign bodies ***(Mok and Piesowicz 1993).***
- Vocal cord dysfunction ***(Place et al., 2000).***
- Obstructive lung disease, particularly COPD or non obstructive lung disease (e.g., diffuse parenchymal lung disease).
- Non-respiratory causes of symptoms (e.g., left ventricular failure).

Careful assessment and treatment of both the asthma and the co- morbidity is often necessary to establish the contribution of each to a patient's symptoms ***(GINA 2006)***.

CLASSIFICATION:

Global Initiative for Asthma ***(GINA 2006)*** subdivided asthma by severity based on the level of symptoms, airflow limitation, and lung function variability into four categories: Intermittent, Mild Persistent, Moderate Persistent, or Severe Persistent ***(GINA 2006).***

I – Intermittent:

- Symptoms less than once a week
- Brief exacerbations
- Nocturnal symptoms not more than twice a month
- FEV1 or PEF ≥ 80% of predicted
- PEF or FEV1 variability < 20%

II - Mild Persistent:

- Symptoms more than once a week but less than once a day
- Exacerbations may affect activity and sleep
- Nocturnal symptoms more than twice a month
- FEV1 or PEF ≥ 80% of predicted
- PEF or FEV1 variability < 20 – 30%

III - Moderate Persistent:

- Daily symptoms
- Exacerbations may affect activity and sleep
- Nocturnal symptoms more than once a week
- Daily use of inhaled short-acting β_2-agonist
- FEV1 or PEF 60-80% of predicted
- PEF or FEV1 variability > 30%

IV - Severe Persistent:

- Daily symptoms
- Frequent exacerbations
- Frequent nocturnal asthma symptoms
- Limitation of physical activities
- FEV1 or PEF ≤ 60% predicted
- PEF or FEV1 variability > 30%

ASTHMA PREVENTION

Measures to prevent asthma may be aimed at the prevention of allergic sensitization (i.e., the development of atopy, likely to be most relevant prenatally and perinatally), or the prevention of asthma development in sensitized people. It may be achieved by several mechanisms ***(GINA 2006)***;

- Allergic sensitization can occur prenatally ***(Bousquet et al., 2000 & Jones et al., 2000).*** There is currently insufficient information on the critical doses and timing of allergen exposure to permit intervention in this process, and no strategies can be recommended to prevent allergic sensitization prenatally ***(GINA 2006)***.

- Breast-feeding and its relation to the development of asthma has been extensively studied and, in general, infants fed formulas of intact cow's milk or soy protein compared with breast milk have a higher incidence of wheezing illnesses in early childhood ***(Friedman and Zeiger 2005)***. Exclusive breast-feeding during the first months after birth is associated with lower asthma rates during childhood ***(Gdalevich et al., 2001)***.

- The "hygiene hypothesis" of asthma, though controversial, has led to the suggestion that strategies to prevent allergic sensitization should focus on

redirecting the immune response of infants toward a Th1, nonallergic response or on modulating T regulator cells ***(Robinson et al., 2004)***, but such strategies still require further investigation. The role of probiotics in the prevention of allergy and asthma is also unclear ***(Isolauri et al., 2001)***. Exposure to cats has been shown to reduce risk of atopy in some studies ***(Ownby et al., 2002)***.

- Avoidance of exposure to indoor allergens; domestic mites, furred animals, cockroaches ***(Morgan et al., 2004)*** and fungi or outdoor allergens, occupational exposures and food additives ***(Roberts et al., 2003)***.

- Exposure to tobacco smoke both prenatally and postnatally is associated with measurable harmful effects, including effects on lung development ***(Martinez et al., 1995)*** and a greater risk of developing wheezing illnesses in childhood ***(Dezateux et al., 1999)***. Passive smoking increases the risk of allergic sensitization in children ***(Strachan and Cook 1998 & Strachan and Cook 1997)***. Both prenatal and postnatal maternal smoking is problematic ***(Kulig et al., 1999)***.

- Avoidance of some medications as aspirin and other non-steroidal anti-inflammatory drugs ***(Szczeklik et al., 2001)***. Beta-blocker drugs

administered orally or intraocularly may exacerbate bronchospasm *(Covar et al., 2005)*.

- Avoidance of obesity: Increases in body mass index (BMI) have been associated with increased prevalence of asthma, although the mechanisms behind this association are unclear ***(Tantisira et al., 2003)***.

- Avoidance of emotional stress may lead to decrease in asthma exacerbations, primarily because extreme emotional expressions (laughing, crying, anger, or fear) can lead to hyperventilation and hypocapnia, which can cause airway narrowing ***(Sandberg et al., 2000 & Rietveld et al., 1999)***.

MANAGEMENT OF ASTHMA

Management consists of a daily treatment plan and an asthma action plan. These plans help the child and his parents to meet treatment goals which include ***(GINA 2006)***:

- Minimize long-term lung damage by treating the underlying inflammation in the lungs.

- Decrease the severity, frequency, and duration of asthma attacks by avoiding triggers.

- Treat acute attacks when they occur.

- Have a high quality of life; the ability to participate in all daily activities, including school, exercise, and recreation-by preventing and managing symptoms.

- Sleep through the night undisturbed by asthma symptoms.

Babies and small children need early treatment for asthma symptoms to prevent severe breathing problems. They may have more serious problems than adults because their bronchial tubes are smaller. Although it may appear that occasional treatment with medications for children with mild asthma is enough, one review has noted that one-third of fatal asthma attacks occurred in children with mild asthma ***(Stempel 2003).***

Some experts suggest using the "rule of two" in treating young children. This states that young children should be treated with long-term medications for persistent asthma if they: ***(Stempel 2003)***

♦ Have symptoms more than 2 times a week.

♦ Awaken at night because of asthma more that 2 times a month.

♦ Use more than 2 canisters of a quick-relief medication per year.

The National Asthma Education and Prevention Program (NAEPP) ***(National Institutes of Health 2002)*** recommends treatment with long-term medications for infants and young children who:

► Consistently need treatment for symptoms more than 2 times per week.

► Have severe attacks more than once every 6 weeks that require an inhaled bronchodilator more than every 4 hours over a 24-hour period.

► Have asthma attacks more than 3 times per year lasting longer than 1 day and affecting sleep and who have parents with a history of asthma or atopic dermatitis

OR two of the following three symptoms:

◊ Wheezing not associated with colds

◊ Allergic rhinitis

◊ High eosinophil count (greater than 4%)

Management of asthma in children involves medications as relievers and controllers as well as simple educational interventions (designed to teach self-management skills) among children admitted to the hospital with asthma which have been shown to significantly reduce the readmission rate and reduce morbidity ***(Guevara et al., 2003).***

- Reliever treatments include inhaled anticholinergics, short-acting oral β_2-agonists, some long-acting β_2-agonists, and short-acting theophylline. Regular dosing with short and long-acting β_2-agonist is not advised unless accompanied by regular use of an inhaled glucocorticosteroid ***(GINA 2006)***.

- Controller medications for children include inhaled and systemic glucocorticosteroids, leukotriene modifiers, long-acting inhaled β_2-agonists, theophylline, cromones, and long-acting oral β_2-agonists ***(GINA 2006)***.

Inhaled therapy is the cornerstone of asthma treatment for children of all ages. Almost all children can be taught to effectively use inhaled therapy. Different age groups require different inhalers for effective therapy, so the choice of inhaler must be individualized (Table 1) ***(GINA 2006).***

Table 1: Choosing an Inhaler Device for Children with Asthma*

Age Group	Preferred Device	Alternate Device
Younger than 4 years	Pressurized metered-dose inhaler + dedicated spacer with face mask	Nebulizer with face mask
4 – 6 years	Pressurized metered-dose inhaler + dedicated spacer with mouthpiece	Nebulizer with mouthpiece
Older than 6 years	Dry powder inhaler or breath-actuated pressurized metered-dose inhaler, or Pressurized metered-dose inhaler + spacer and mouthpiece	Nebulizer with mouthpiece

**Based on efficacy of drug delivery, cost effectiveness, safety, ease of use, and convenience.*

** GINA guidelines 2006.

A - Inhaled glucocorticosteroids:

Inhaled glucocorticosteroids are the most effective controller therapy for asthma in children of all ages. (Table 2) lists approximately equipotent doses of different inhaled glucocorticosteroids administered via different inhalation devices ***(GINA 2006)***.

Table 2:

Estimated Equipotent Daily Doses of Inhaled Glucocorticosteroids for Children†

Drug	Low Daily Dose (µg)	Medium Daily Dose (µg)	High Daily Dose (µg) ‡
Beclomethasone dipropionate	100-200	>200-400	>400
Budesonide*	100-200	>200-400	>400
Ciclesonide*	80-160	>160-320	>320
Flunisolide	500-750	>750-1250	>1250
Fluticasone	100-200	>200-500	>500
Mometasone furoate*	100-200	>200-400	>400
Triamcinolone acetonide	400-800	>800-1200	>1200

† Comparisons based upon efficacy data.
‡ Patients considered for high daily doses except for short periods should be referred to a specialist for assessment to consider alternative combinations of controllers. Maximum recommended doses are arbitrary but with prolonged use are associated with increased risk of systemic side effects.
** Approved for once-daily dosing in mild patients.*
** GINA guidelines 2006.

Some patients require higher doses (400 µg/day) to achieve optimal asthma control and effective protection against exercise-induced asthma. Only a minority of patients require treatment with high doses of inhaled glucocorticosteroids ***(Adams et al., 2005 & Powell and Gibson 2004).***

Treatment with inhaled glucocorticosteroids in children 5 years and younger with asthma generally produces similar clinical effects as in older children, but dose-response relationships have been less well studied ***(Roorda et al., 2001).***

- ***Side effects;*** the majority of studies evaluating the systemic effects of inhaled glucocorticosteroids have been undertaken in children older than 5 years.

- ***Growth:***

Uncontrolled or severe asthma adversely affects growth and final adult height. No long-term controlled studies have reported any statistically or clinically significant adverse effects on growth of 100 to 200 µg per day of inhaled glucocorticosteroids but only when a high dose is administered ***(Agertoft and Pedersen 2000).***

Different age groups seem to differ in their susceptibility to the growth-retarding effects of inhaled glucocorticosteroids; children aged 4 to 10 years are more susceptible than adolescents ***(Sharek and Bergman 2000).***

Children with asthma treated with inhaled glucocorticosteroids attain normal adult height (predicted from family members) but at a later age ***(Pedersen 2001).***

- ***Bones:***

No studies have reported any statistically significant increased of risk of fractures in children taking inhaled glucocorticosteroids ***(The Childhood Asthma Management Program Research Group 2000)***, while use of oral or systemic glucocorticosteroid increases the risk of fracture along with the number of the treatments ***(van Staa et al., 2003)***.

Steroid-induced osteoporosis results from the inhibition of osteoblastic activity, increased bone resorption due to attenuated sex hormone secretion, and raised parathyreoid hormone levels due to reduced renal and gastrointestinal calcium absorption ***(Lipworth 1999)***.

Controlled longitudinal studies of 2 to 5 years' duration and several cross-sectional studies found no adverse effects of inhaled glucocorticosteroid treatment on bone mineral density, no prospective studies have followed children on inhaled glucocorticosteroid treatment until peak bone mineral density has been reached ***(van Staa et al., 2004)***.

The problems of studying a potential adverse effect of ICS on BMD are very similar to those of studying the effect of ICS on growth. The duration of therapy and the interval for assessing BMD in clinical trials is usually very short, differences in BMD which might be attributed to ICS may not be clinically relevant. Finally, physical activity might be affected by improved asthma treatment, which in turn has +ve or -ve effect on long-term changes in BMD (***Schlienger et al., 2004***).

Additionally complicating the matter is that BMD is constantly changing throughout life, increasing over time until early adulthood and then gradually declining, with accelerating decline in older ages. The effect of ICS on BMD may be different when the body is building up BMD at younger ages versus when BMD is generally declining at older ages. A subtle effect on BMD would not become clinically relevant until it was additive to other risk factors, such as age. Any effect possibly attributable to childhood use of ICS might be confounded by continued use of ICS into adulthood. ***(Kemp et al., 2004, Pauwels et al., 2003, Roux et al., 2003& Agertoft and Pedersen 1998).***

- ***Oral candidiasis, hoarseness, and bruising:***

Clinical thrush is seldom a problem in children treated with inhaled or systemic glucocorticosteroids. This side effect seems to be related to concomitant use of antibiotics, high daily doses, dose frequency, and inhaler device. Spacers reduce the incidence of oral candidiasis ***(Selroos et al., 1994)***. Mouth rinsing is beneficial ***(Randell et al., 2003).***

- ***Hypothalamic-pituitary-adrenal (HPA) axis:***

Inhaled glucocorticosteroid doses of less than 200 µg budesonide or equivalent doses daily are normally not associated with any significant suppression of the HPA axis in children ***(The Childhood Asthma Management Program Research Group 2000).*** At higher doses, small changes in HPA axis function can be detected with sensitive methods ***(Kemp et al., 2004)***.

B- Leukotriene modifiers:

They provide clinical benefit in children older than 5 years at all levels of severity ***(Szefler et al., 2005, Ostrom et al., 2005, Garcia Garcia et al., 2005 & Ng et al., 2004)*** , but generally less than that of low-dose inhaled glucocorticosteroids ***(Vidal et al., 2001).*** Leukotriene modifiers provide partial protection against exercise-induced bronchoconstriction within hours after administration ***(Vidal et al., 2001& Kemp et al., 1998).***

As add-on treatment in children whose asthma is insufficiently controlled by low doses of inhaled glucocorticosteroids, leukotriene modifiers provide moderate clinical improvements, including a significant reduction in exacerbations ***(Phipatanakul et al., 2004 & Simons et al., 2001).***

In cases of children 5 years and younger, in addition to the efficacy as described above ***(Knorr et al., 2001),*** leukotriene modifiers reduce viral induced asthma exacerbations in children ages 2-5 with a history of intermittent asthma ***(Bisgaard et al., 2005).***

C - Long-acting inhaled β_2-agonists:

Long-acting inhaled β_2-agonists are primarily used as add-on therapy in children older than 5 years whose asthma is insufficiently controlled by medium doses of inhaled glucocorticosteroids or as single dose therapy before vigorous exercise. Monotherapy with long-acting inhaled β_2- agonists should be avoided ***(Nelson et al., 2006).***

Add-on treatment with long-acting inhaled β_2-agonists has not been shown to reduce the frequency of exacerbations. Inhalation of a single dose of long-acting inhaled β_2 agonist effectively blocks exercise-induced bronchoconstriction for several hours ***(Simons 1997).*** Combination products containing an inhaled glucocorticosteroid and a long-acting inhaled β_2-agonist are preferred to long-acting inhaled β_2-agonist and inhaled glucocorticosteroids administered by separate inhalers. Fixed combination inhalers ensure that the long-acting β_2-agonist is always accompanied by a glucocorticosteroid ***(Bisgaard 2003)***.

In children 5 years or younger, the effect of long-acting inhaled β_2-agonists or combination products has not yet been adequately studied ***(GINA 2006).***

D –Theophylline:

Theophylline has been shown to be effective as monotherapy and as add-on treatment to inhaled or oral glucocorticosteroids in children older than 5 years ***(Katz et al., 1978).***

Maintenance treatment offers a marginal protective effect against exercise-induced bronchoconstriction ***(Magnussen 1988).*** Add-on treatment with theophylline has been found to improve asthma control and reduce the maintenance glucocorticosteroid dose necessary in children with severe asthma treated with inhaled or oral glucocorticosteroids ***(Brenner et al., 1988 & Nassif et al., 1981).***

E - Cromones: sodium cromoglycate and nedocromil sodium.

They have a limited role in the long-term treatment of asthma in children. Nedocromil sodium has been shown to reduce exacerbations, but its effect on other asthma outcomes is not superior to placebo ***(The Childhood Asthma Management Program Research Group 2000).*** A single dose of sodium cromoglycate or nedocromil sodium attenuates bronchospasm induced by exercise or cold air ***(Spooner et al., 2000).***

F - Long-acting oral β_2-agonists:

Treatment with long-acting oral β_2-agonist such as slow release formulations of salbutamol, terbutaline, and bambuterol reduces nocturnal symptoms of asthma ***(Kuusela et al., 2000 & Zarkovic et al., 2000).*** Due to their potential side effects of cardiovascular stimulation, anxiety, and skeletal muscle tremor, their use is not encouraged. If used, dosing should be individualized, and the therapeutic response should be monitored to limit its side effects ***(Lonnerholm et al., 1984).***

G - Systemic glucocorticosteroids:

Because of the side effects of prolonged use, oral glucocorticosteroids in children with asthma should be restricted to the treatment of acute severe exacerbations, whether viral-induced or otherwise ***(GINA 2006).***

Medical checkups

Children need to monitor their asthma and have regular checkups to keep asthma under control (Table 3) and to ensure correct treatment. The frequency of checkups depends on how the child asthma is classified. Checkups are recommended on the following frequencies ***(Partridge and Hill 2000)***:

♦ About every 6 to 12 months for children with mild intermittent or mild persistent asthma that has been under control for at least 3 months.

♦ Every 3 to 4 months for children with moderate persistent asthma.

♦ Every 1 to 2 months for children with uncontrolled or severe persistent asthma.

During checkups, health professional should check to see that all goals are being met and to ensure that management plan is going in the right way (Figure 1). Parents and children should be asked whether symptoms and peak expiratory flow have held steady, improved, or become worse, and about asthma attacks during exercise, at night, or after laughing or crying hard. This information should be tracked in an asthma diary. The child may be asked to bring the peak expiratory flow meter to an appointment so the health professional can see how he or she uses it ***(Gibson and Powell 2004 & Fishwick et al., 1997)***.

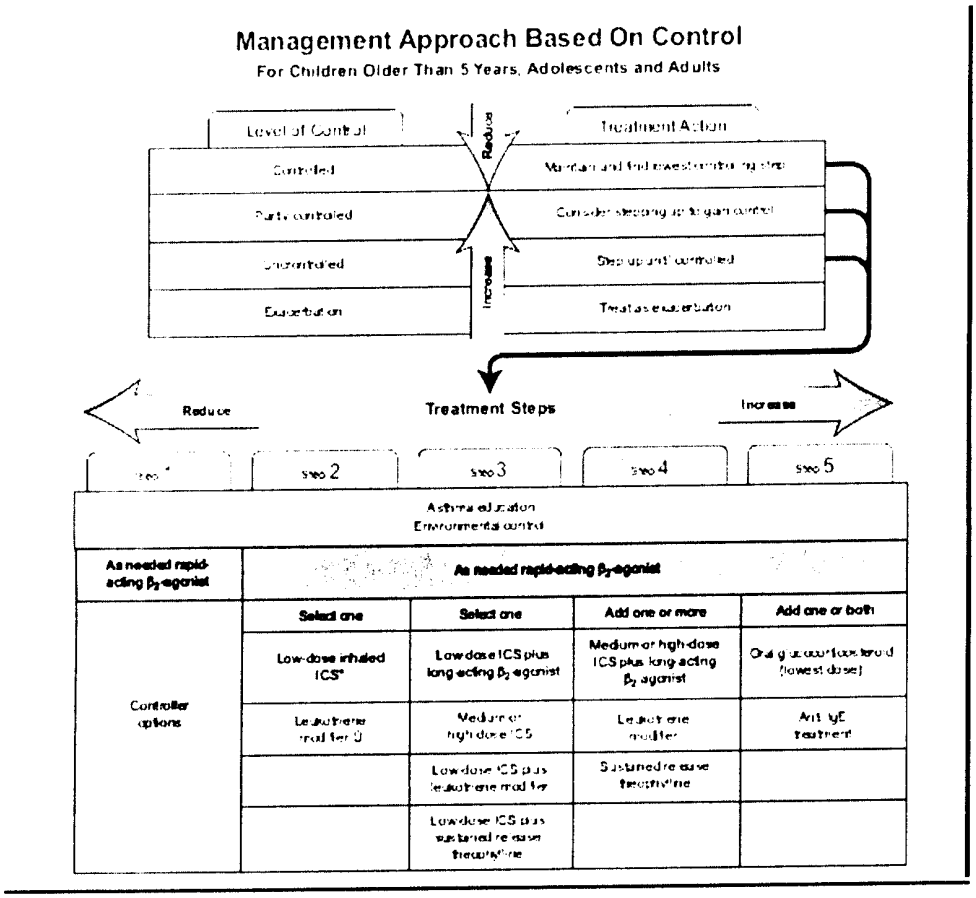
Table 3: Levels of Asthma Control

Characteristic	Controlled (All of the following)	Partly Controlled (Any measure present in any week)	Uncontrolled
Daytime symptoms	None (twice or less / week)	More than twice/week	Three or more features of partly controlled asthma present in any week
Limitation of activities	None	Any	
Nocturnal symptoms /awakening	None	Any	
Need for reliever/ rescue treatment	None	More than twice/week	
Lung function (PEF or FEV_1)‡	Normal	< 80% predicted or personal best (if known)	
Exacerbations	None	One or more / year*	One in any week†

* *Any exacerbation should promote review of maintenance treatment to ensure that it is adequate.*
† *By definition, an exacerbation in any week makes that an uncontrolled asthma week*
‡ *Lung function is not a reliable test for children 5 years and younger.*

** GINA guidelines 2006.

Figure 1: ** GINA guidelines 2006.



* ICS=inhaled glucocorticosteroids
Ü=Receptor antagonist or synthesis inhibitors

Alternative reliever treatments include inhaled anticholinergics, short-acting oral β_2-agonists, some long-acting β_2-agonists, and short-acting theophylline. Regular dosing with short and long-acting β_2-agonist is not advised unless accompanied by regular use of an inhaled glucocorticosteroid.

CHAPTER II

Bone Mineral Density

The critical processes of skeletal growth and bone mineralization take place during childhood. A thorough understanding of these processes should be obtained for two reasons. First, attainment of peak bone mass (PBM) by early adulthood is a central element in the prevention of adult-onset osteoporosis .

Second, reduced BMD may increase the risk for fractures in children and adolescents. Both bone mass accumulation and longitudinal growth of one are complex processes controlled by genetic and environmental factors as well as hormonal signals, many of which have become better understood in the past 25 years ***(Heaney et al., 2000)***.

Throughout most of childhood, bone mass and longitudinal growth are closely related: as the skeleton increases in length (height), it also increases in mass. During puberty, however, a disparity between these factors develops whereby increases in bone mass lag behind increases in height ***(Martin et al., 1997)***.

A prospective study of 140 boys and girls evaluated by DEXA demonstrated that the rate of bone mineral uptake in the femoral neck, lumbar spine, and total body does not reach a maximum until at least 1 year after peak height velocity (PHV) is achieved ***(Bailey 1997).***

Skeletal growth also has been demonstrated to vary by anatomic location.during early childhood, the rate of appendicular growth outpaces the rate of axial bone growth. This relationship then reverses during puberty, when axial skeletal growth accelerates while appendicular growth remains constant ***(Bonjour et al., 1997 & Theintz et al., 1992)***.

Hormonal factors such as insulin-like growth factor 1 (IGF-1), growth hormone, and sex hormones likely mediate these mechanisms via site-specific end organ receptors ***(Martin et al., 1997)***.

BMD measured in various skeletal regions can be broadly grouped into two types: cortical bone and trabecular bone. For instance, the lumbar spine contains both trabecular and cortical bone, and the femoral neck contains largely trabecular bone ***(Nguyen et al., 2000).***

Bone densitometry has demonstrated that bone mass accumulation also varies by region. In a longitudinal study of girls aged 11 to 14 years and boys aged 13 to 17 years, showed that increases in bone mass in the lumbar spine and femoral neck were three times that found in the mid femoral shaft ***(Theintz et al., 1992).***

A clear distinction between bone mass (or content) and BMD is critical in analyzing developmental studies because simple bone mass increases may reflect the increased bone size (cortical shell thickness) that occurs during growth rather than increased density (mass per unit volume). The increase in BMC of the lumbar spine during puberty, for example, is almost 10 times greater than the corresponding mean increase in volumetric trabecular density of the vertebrae ***(Martin et al., 1997)***.

To control for differences between the sexes that occur during puberty, the BMC of healthy children at the age of PHV was examined and demonstrated that, at the age of PHV, both boys and girls have achieved approximately 70% of their adult BMC in the femoral neck and 60% of their adult BMC in the lumbar spine as well as total body. It also showed that whereas boys have higher BMC at all skeletal sites because of their larger skeletons, the percentage of adult BMC attained did not differ between the sexes. According to these data, it appears that boys enter young adulthood with greater overall skeletal mass because of their larger bone size, but BMD in boys is not drastically different from that in girls ***(Bailey 1997)***.

Bone mineral density (BMD) is determined by many demographic and lifestyle factors, such as sex, age, height, weight, dietary calcium intake, and physical activity ***(Bonjour et al., 1991).***

While reduced BMD has been reported in asthmatic adults treated with ICS, ***(Packe et al., 1996)*** results of studies in children suggest that these agents do not have adverse effects on BMD measured using dual energy *x* ray absorptiometry (DEXA) ***(Efthimiou and Barnes 1998).***

High doses of oral steroids have been shown to adversely affect bone mineral density in adults and in children ***(Toogood et al., 1995 & Prince et al., 1991)***. However, when given to patients with severe disease such treatment may sometimes increase bone mineral density, probably because of changes in physical activity or diet and/or improvement in disease control. This makes prediction of the effects of exogenous steroids on the asthma disease is difficult ***(Reid et al., 1986)***.

FACTORS INFLUNCING SKELETAL MINERALIZAION:

Many factors have been encountered in studies of bone mineralization; genetics, calcium intake, vitamin D, proteins and sodium also were included. Aside from these factors that influence the effect of milk and other dairy products on bone, exercise levels, body weight and pubertal status must be controlled or accounted for in studies of bone integrity ***(National Institutes of Health, Osteoporosis Prevention, Diagnosis, and Therapy 2000)***.

I - Genetics:

Genetic studies of osteoporosis and its major risk factors represent one of the most rapidly developing areas for research in genetic epidemiology and bone biology. It is obvious now that the variation in BMD, a primary predictor of fracture risk, among individuals is largely regulated by genetic factors (***Liu et al., 2003, Peacock et al., 2002 & Livshits et al., 1998).***

The covariation in BMD measures in different skeletal sites, predominantly at the lumbar spines and femoral neck, is also under genetic influence, probably because of a pleiotropic effect or close linkage and linkage disequilibrium of the respective genes ***(Nguyen et al., 1998)***.

The covariation in BMD at these sites have substantial genetic determinants in common (pleiotropy or close linkage and linkage disequilibirum), with a considerable evidence of shared environmental effects. The pleiotropic effect, if it exists, may be controlled by a major genetic locus. This major gene is likely involved into a regulation of variation of BMD at different skeletal sites. However, the magnitude of its effect is site dependent. The residual BMD variation may be attributable to polygenic component ***(Livshits et al., 2004).***

However, the real genetic transmission of quantitative traits may even be more complex. Various interactions between genes, genes and age, and

environment (including humoral factors) are also likely to be involved in BMD transmission and may complicate the situation substantially ***(Liu et al., 2003).***

It is quite likely that different polymorphisms (or genes) are responsible for the variation of BMD in different populations. That is, the existence of numerous potentially relevant genes involved in BMD determination cannot be excluded. However, the different mutations with major effect were likely accumulated in various populations. Thus, apart from the possible false positive results obtained in a "whole-genome" scan, different loci are expected to be associated with BMD in different populations ***(Wilson et al., 2003 & Deng et al., 2002)***.

Indeed, whole-genome linkage scans to date have yielded inconsistent results across populations. In the majority of studies, the different DNA markers were associated with BMD at various skeletal sites even within the same pedigrees. For example, femoral trochanter was linked to a 21qter chromosome, and the lumbar spine was linked to a 14q31 chromosome in the Framingham cohort. On the other hand, in most studies, for the given BMD, as a rule, significant linkage to one specific chromosomal segment and a few more (if any) with substantially lower probability were identified ***(Liu et al., 2003 & Karasik et al., 2002)***.

BMD is biologically a complex trait because it is determined by both, and perhaps interaction between, genetic and environmental factors. Several twin and

family studies have shown that the difference in BMD among individuals in a population is largely regulated by genetic factors, with genes accounting for between 65% and 92% of the variance of BMD in any population ***(Peacock et al., 2002 & Nguyen et al., 1998).***

Investigations have identified specific DNA polymorphisms of the vitamin D receptor that predict differences in BMD in prepubertal children as well as adults. Using DEXA to determine the BMD of 250 healthy monozygotic and dizygotic twins, clearly demonstrated a co dominant effect of two specific allelic variants, which they designated B and b. BMD was significantly and proportionately lower in homozygotic BB and heterozygotic Bb individuals than in homozygotic bb individuals ***(Morrison et al., 1994)***.

The importance of genotype in predicting BMD phenotype also has been corroborated in children. Specific allelic variations at the vitamin D receptor in prepubertal girls appeared to correlate with differences in BMD when measured by QCT but not with cross-sectional area or cortical thickness. Children with the bb genotype demonstrated significantly higher BMD in the femur and vertebrae than did children with the BB genotype. Importantly, this genotypic variation does not correlate with any observable differences in developmental status ***(Sainz et al., 1997)***.

II – Calcium:

The National Academy of Sciences has recommended that adequate dietary intake of calcium is necessary in children and adolescents for the development of peak bone mass and prevention of fractures and osteoporosis later in life ***(Institute of Medicine, Food and Nutrition Board 1997).***

The current recommended adequate intake for children 9 to 18 years of age is 1300 mg/day, which is higher than that in other developed countries ***(Lanou et al., 2005).*** This recommended intake is based largely on the results of calcium-balance studies that show that in healthy children of this age, maximal net calcium balance is achieved with this intake ***(Abrams et al., 1997).*** At higher levels of intake, additional calcium is mostly excreted. Peak calcium accretion is attained at the ages of 12.5 years in girls and 14.0 years in boys ***(Baily et al., 2000).***

Despite this, the percent of children achieving the recommended adequate calcium intake in the United States declines dramatically after the second year of life, reaching its nadir between 12 and 19 years of age, when documented intakes in this age group approximate only 700 to 1000 mg/day ***(Lanou et al., 2005, Suitor et al., 2002, US Department of Agriculture 1999, Institute of Medicine, Food and Nutrition Board 1997).***

In fact, only 10% of adolescent girls achieve the recommended adequate dietary intake of calcium. By using measures of bone health (fracture rate and radiologic measures of bone mineralization and bone strength) rather than calcium-balance studies, an intake of 1300 mg/day is not warranted ***(Lanou et al., 2005)***.

There is no direct evidence that calcium supplements at any level in childhood or adolescent have any impact on long-term bone health in adults, including osteoporosis. Even when using radiologic measures of bone health rather than calcium-balance studies, it is difficult to show a positive effect of calcium intake alone on bone mineral over the short term. Calcium intake of 1300 mg/day is advised, and the National Academy of Sciences has set an upper limit of 2500 mg/day for this age group. The easiest way to achieve this level of intake is to consume dairy products. In light of our ongoing concerns about pediatric obesity, low-fat dairy products would be preferred ***(Kardinaal et al., 1999& Seppa 1994)***.

In addition, with dairy products, many other beneficial nutrients should be supplied to this age group including vitamin D, generally not available from other dietary sources. It is interesting to note that longitudinal calcium intake has recently been negatively correlated with percent body fat in children ***(Skinner et al., 2003 & Carruth and Skinner 2001).***

Numerous nutrition policy statements recommend the consumption of 800 to 1500 mg of calcium largely from dairy products for osteoporosis prevention; however, the findings of epidemiologic and prospective studies have raised questions about the efficacy of the use of dairy products for the promotion of bone health. The objective of many studies was to review existing literature on the effects of dairy products and total dietary calcium on bone integrity in children and young adults to assess whether evidence supports current recommended calcium intake levels and the suggestion that dairy products are better for promoting bone integrity than other calcium-containing food sources or supplements ***(National Institutes of Health, Osteoporosis Prevention, Diagnosis, and Therapy 2000 & National Institutes of Health., Optimal calcium intake JAMA 1994)***.

Over the past 20 years, the National Institutes of Health, the National Academy of Sciences, and the US Department of Agriculture have made recommendations for calcium intake for children and adults for the intended purpose of osteoporosis prevention. Recommended intakes have escalated gradually, and dairy products have been promoted often in federal nutrition policy documents as a "preferred" calcium source ***(US Department of Agriculture and US Department of Health and Human Services 2000& US Department of Agriculture, The Food Guide Pyramid 1996).***

However, because the level of dairy product consumption in the United States is among the highest in the world, accounting for 72% of dietary calcium intake, and osteoporosis and fracture rates are simultaneously high, (***Gerrior and Bente 2001 & Abelow et al., 1992***) numerous researchers have called into question the effectiveness of nutrition policies aimed at osteoporosis prevention through dairy consumption (***Hegsted 2001, Weinsier and Krumdieck 2000 & Avenell 1994).***

Findings from recent epidemiologic and prospective studies in women, children, and adolescents also have raised questions about the efficacy of the use of dairy products and other calcium-containing foods for the promotion of bone health ***(Feskanich et al., 2003, Lloyd et al., 2002, Lloyd and Taylor 2001, Lloyd et al., 2000 & Kröger et al., 1993)*** .

The World Health Organization's recommendations for preventing osteoporosis, published in 2003, acknowledge this "calcium paradox" and recommend a minimum intake of 400 to 500 mg/day of calcium from all sources for individuals who live in countries with a high fracture incidence and are 50 years of age and older(***Joint Food and Agriculture Organization of the United Nations/World Food Organization of the United Nations Expert Consultation on Diet, Nutrition, and the Prevention of Chronic Diseases 2003).***

Furthermore, the World Health Organization report concluded that "there is no case for global, population-based approaches." This report did not include a recommended minimum intake for children and adolescents. These findings contrast with European, UK, and other dairy-consuming nations' calcium recommendations (Table 4), including the US adequate intakes, which recommend between 800 and 1300 mg/day of calcium for all individuals in the United States across the lifespan ***(Institute of Medicine, Food and Nutrition Board 1997).***

Table 4: Current Calcium Intake Requirements for Children and Adolescents

	European Union 1993 Population Reference Intake, mg/d	UK 1991 Reference Nutrient Intake, mg/d	Australia 1991 Recommended Dietary Intake, mg/d	US and Canada 1997 Adequate Intake, mg/d
Infancy	400	525	300 (human)	210–270
			500 (cow)	
Childhood	400–550	350–550	530–800	500–800
Puberty and adolescence				
Boys	1000	1000	1000–1200	1300
Girls	800	800	800–1000	1300

Source: ***Report of the Joint Food and Agriculture Organization of the United Nations/World Food Organization of the United Nations Expert Consultation on Human Vitamin and Mineral Requirements, September 1998. Available at: ftp://ftp.fao.org/es/esn/nutrition/Vitrni/vitrni.html.***

A study of healthy American children, showed that only 15% of children over 11 years of age obtain the recommended daily allowance (RDA) for calcium and that intake of >1,000 mg daily correlated with higher BMC than did lower intake (P = 0.001) ***(Chan 1991)***.

Similarly, the Centers for Disease Control and Prevention reported that females over 12 years of age of almost all racial and ethnic groups consume less than the RDA for calcium ***(Alaimo et al., 1988)***. These figures are remarkable, given the amount of evidence unequivocally supporting adequate dietary calcium before, during, and after puberty as possibly the only modifiable factor for reaching peak BMD ***(Bonjour et al., 1997 & Lee et al., 1994)***.

By studying identical twin pairs, investigators have demonstrated that adequate dietary calcium intake in prepubertal children leads to significantly increased BMD at the radius and at the lumbar spine ***(Johnston et al., 1992)***.

In a 3-year, double-blind, prospective study of 45 twin pairs in which one child of each twin pair received calcium supplementation and the other received placebo, children receiving calcium had 2% to 5% greater increases in BMD at all skeletal sites measured ***(Johnston et al., 1992)***.

These findings have been corroborated by other randomized, placebo-controlled studies in prepubertal children. The beneficial effects of calcium supplementation are more profound at appendicular skeleton locations ***(Bonjour et al., 1997).***

Children accustomed to a low calcium diet had greater increases in BMD with calcium supplementation than did children with adequate calcium intake at baseline ***(Lee et al., 1994).*** Calcium intake follows a threshold pattern; increased intake correlates with increased calcium balance until a limit is reached at which increases do not result in further net increases in calcium storage ***(Matkovic and Heaney 1992).***

Because this threshold was found to exceed previous RDAs, recommendations were modified in 1994 to 400 to 600 mg of calcium per day for infants from birth to 1 year of age, 800 to 1,200 mg per day in children aged 1 to 10 years, and 1,200 to 1,500 mg per day for adolescents and young adults aged 11 to 24 years ***(NIH Consensus Conference, Optimal Calcium Intake JAMA 1994).***

Equate amounts of dietary calcium are relatively easy to obtain, with one cup of milk (250 ml) containing 300 mg of calcium, and the risks related to increased calcium intake are minimal. In addition to dairy products, other good food sources of calcium include certain green vegetables, such as broccoli and

kale, calcium-set tofu, seeds, nuts, and fortified food products such as orange juice ***(Report of a Joint Food and Agriculture Organization of the United Nations/World Food Organization of the United Nations Expert Consultation 1998).***

Given the importance of adequate calcium intake in achieving PBM, the likelihood of poor intake during adolescence, and the safety of supplementation, increasing calcium intake should be emphasized to all teenage patients and their families ***(Joint Food and Agriculture Organization of the United Nations/World Food Organization of the United Nations Expert Consultation on Diet, Nutrition, and the Prevention of Chronic Diseases 2003)***..

The National Institutes of Health has identified low calcium intake as a critical public health concern requiring public education programs as well as private and public sector initiatives to address socioeconomic, ethnic, age, sex, and regional barriers to optimization ***(NIH Consensus Conference, Optimal Calcium Intake JAMA 1994).***

When designing studies to quantify the effect of the consumption of milk and dairy products on bone mineral density (BMD), bone mineral content (BMC), calcium balance, and, ultimately, peak bone mass, it is important to control for factors that may influence these indices of bone health ***(Lanou et al., 2005).***

III - Vitamin D:

Vitamin D is essential for calcium uptake and bone development and remodeling. The primary source of vitamin D is conversion in the skin, via exposure to UVB radiation, of 7-dehydrocholesterol to vitamin D_3, which then is metabolized sequentially in the liver and the kidney to its active form, 1, 25-dihydroxyvitamin D. Few studies have investigated the effect of vitamin D intake, sun exposure, or vitamin D status on bone mineral in children and young adults ***(Holick 1996)***.

In a 3-years prospective study of girls aged 9 to 15 years, baseline concentration of serum 25-hydroxyvitamin D was associated positively with a 3-year change in BMD at the lumbar spine and femoral neck. Girls with hypovitaminosis D had a 4% lower BMD accumulation from baseline than did girls with normal vitamin D status ***(Lehtonen-Veromaa et al., 2002).***

Cow milk sold in the United States is supplemented with vitamin D precursors, although this is not generally true for other countries or for other dairy products. Studies that evaluate effects of US milk consumption on bone health, therefore may, be confounded by the presence of supplemental vitamin D ***(US Department of Agriculture and US Department of Health and Human Services 2000)***.

IV – Proteins:

Dietary protein, including that from dairy products, influences calcium balance. An adequate protein intake is important for supporting bone growth in children ***(Cromer and Harel 2000)*** and maintaining bone mass in older adults ***(Promislow et al., 2002 & Hannan et al., 2000).***

However, increasing intake of dietary protein, particularly animal protein, is associated with increased urinary calcium losses ***(Breslau et al., 1988)*** that may result in increased bone resorption ***(Barzel and Massey 1998)*** or increased fracture. ***(Frassetto et al., 2001)*** In metabolic studies, doubling protein intake produces an ~50% increase in urinary calcium ***(Heaney and Recker 1982).*** Approximately 6 mg of dietary calcium is theoretically required to offset the urinary calcium loss associated with 1 g of protein ***(Weaver et al., 1999).***

V – Sodium:

Dairy products may contain up to 20% of the recommended dietary allowance for sodium. Sodium is an important determinant of urinary calcium excretion because the two minerals compete for resorption in the renal tubules ***(Nordin 1997 & Matkovic et al., 1995).***

For every 2300 mg of sodium excreted by the kidney, 40 to 60 mg of calcium also are lost (i.e., every 100 mmol of sodium excreted leads to the excretion of ~1 mmol of calcium) ***(Nordin et al., 1993).***

In one study, urinary calcium excretion was shown to be negatively associated with bone mineral density in 8- to 13-year-old girls,*(Matkovic et al., 1995)* but in another study, salt intake was not associated with bone mass of prepubertal children. The difference in the calcium : sodium ratio of the diets may be responsible for these differing findings *(Jones et al., 2001)*.

VI – Physical Activity:

Physical activity is an important modulator of skeletal health. Physical activity levels during ages 12 to 18 have been shown to exert a greater influence on later adult bone mineral density and risk for hip fracture than does calcium intake during these ages *(Lloyd et al., 2002, Lloyd et al., 2000 & Nieves et al., 1992).*

By using radiologic measures of bone health, physical activity is the most important modifiable factor that determines increased bone growth and development in adolescents *(Lanou et al., 2005).*

Only exercise history (participation in sports), rather than calcium intake, was significantly correlated with bone mineral density and bone strength. It is well known that weight-bearing exercise plays a role in achieving maximal peak bone mass, but data to quantify the effect are limited *(Du et al., 2002, Uusi-Rasi et al., 1997, Gunnes and Lehmann 1996 & Ruiz et al., 1995)*.

It is unclear, however, whether any given level of calcium intake influences the degree of benefit derived from exercise on bone mass or whether exercise alone, independent of calcium intake, improves bone mass. Although one could speculate that less-active people need more calcium in their diets than active ones, a study found no interaction between calcium intake and physical activity ***(Lloyd et al., 2004).***

This is in contrast to another recent report from the United Kingdom. In this cross-sectional study of 38 girls and 38 boys between 8 and 11 years of age, there was a synergistic effect on bone density of a calcium intake of 700 to 800 mg/day and vigorous exercise (25–40 minutes per day) ***(Rowlands et al., 2004).***

Pediatric care providers should continue to promote physical activity and optimal calcium intake in childhood and adolescence, with the anticipation that if these healthy lifestyle practices are instituted early in childhood, they will continue throughout a lifetime ***(Hara et al., 2001, Bass et al., 1998, VandenBergh et al., 1995, Valimaki et al., 1994 & Welten et al., 1994).***

VII – Body Weight:

Body weight has been shown to be a strong predictor of bone mineral content in children ***(Du et al., 2002 & Moro et al., 1996).*** Dairy products are a major source of energy and fat, contributing 18% of total energy and 25% of total fat intake in the diets of children (2–18 years) in the United States ***(Subar et al.,***

1998). Therefore, their impact on bone health may be mediated by their effect on body weight *(Moro et al., 1996).*

The effects of diet on bone mineralization and growth have been well-established during infancy and childhood. Studies suggest that the immediate prepubertal period may be of critical importance in the evolution of osteoporosis of later adult life. There are, however, no data that relates the evolution of adult osteoporosis to diet in late infancy and early childhood *(Kleinman 2000).*

Chemical Regimen (CR)-induced weight loss, but not EX-induced weight loss, is associated with reductions in BMD at clinically important sites of fracture. These data suggest that EX should be an important component of a weight loss program to offset adverse effects of CR on bone *(Villareal et al., 2006).*

VIII – Pubertal Status:

Pubertal status has a profound effect on bone turnover and calcium economy, it is also a predictor of bone mineralization *(Du et al., 2002, Maggiolini et al., 1999, Ruiz et al., 1995 & Sentipal et al., 1991).*

Bone mass increases with age, and its peak value is achieved after puberty *(Bonjour et al., 1994 & Seeman et al., 1993).* It has been suggested that an appropriate timing of puberty is necessary for normal peak BMD acquisition, which may not be achievable in children with CDGP *(Finkelstein et al., 1996, Schoenau 1996 & Seeman et al., 1993).*

Measurement of Bone Mineral Density:

Childhood and adolescence are recognized as critical periods for the attainment of peak bone mass (PBM). Attaining PBM by early adulthood is necessary to reduce the risk of adult-onset osteoporosis, which is a worldwide public health problem and the most common metabolic bone disorder in North America ***(Nevitt 1994).***

Prior to the widespread use of dual-energy x-ray absorptiometry (DEXA), low bone mineral density (BMD) could only be inferred based on nonspecific and insensitive biochemical measurements, a history of fractures, or the appearance of bone on plain radiographs ***(Johnston et al., 1981)***.

DEXA provides a measure of areal bone mineral density (aBMD, mg/cm2) that is calculated by dividing the total (cortical and trabecular) bone mineral content by the projected area of the region of skeleton scanned. As the volume of the scanned bone is not measured, aBMD fails to distinguish between changes in the mineral density and bone size in growing children. This is an important consideration, as chronic childhood asthma may lead to delay in growth and puberty, whereas treatment with high dose of ICS might impair both the growth and mineralization of the skeleton ***(Packe et al., 1996)***.

The recent use of DEXA and other modalities has enabled clinicians and researchers to understand more clearly the physiologic process of skeletal mineralization, define the extent of osteopenia in both the general population and

in children with chronic disorders, and track the efficacy of specific interventions in enhancing BMD ***(Kaufman 1999)***.

Despite the emergence of poor bone mineralization in children as a condition more prevalent than previously recognized, studies on this subject in the orthopaedic literature are lacking. Understanding bone mass accrual and techniques of measurement is critical for the effective evaluation and treatment of patients with subtle and severe presentations of reduced BMD ***(World Health Organization 1994).***

Understanding the units of measurement and differences in types of bone measured is important for drawing conclusions about study results and patient data. Bone mineral content (BMC) is a measurement of bone size and therefore tends to increase as bone grows ***(Kaufman 1999)***.

BMD is calculated by dividing the BMC by the surface area of the region of interest. Often referred to as areal BMD, this two-dimensional result is only an estimation of the true volumetric BMD, which is calculated by correlating BMD data obtained for both anteroposterior (AP) and lateral measurements. Volumetric BMD is seldom reported in the literature.

Radiographs, which are typically the first tests ordered by orthopedic surgeons, cannot provide an accurate quantitative assessment of BMD. Reductions in BMD do not become apparent until at least approximately 30% to 40% of the mineral has been lost. Certain childhood diseases (e.g., rickets) do demonstrate characteristic radiographic findings, so radiographs may be sufficient to diagnose

these conditions.However, radiographs are not a sensitive measure of BMD, so clinicians should not rule out osteopenia based on an apparently normal mineralization pattern on radiographs ***(Johnston et al., 1981).***

During the past 10 years, DEXA has emerged as a cost-effective, safe, and accurate means to quantitate skeletal mass. The World Health Organization has adopted DEXA derived BMD measurements to define normal bone, osteopenia, and osteoporosis (Table 5) ***(World Health Organization 1994).*** Chronic diseases often cause primary osteopenia in children, and as a result of poor nutrition, steroid use, or a combination of factors, these children may develop osteoporosis. BMD standards for pediatric populations have been generated and are incorporated into DEXA software programs for comparisons with an individual patient's measurements ***(Southard et al., 1991).***

Table 5: Definition of Terms relating to Bone Mineral Density*

Condition of Bone	Bone Mineral Density
Normal bone	Within 1 SD of mean for age
Osteopenia	1.0 – 2.5 SD below mean for age
Osteoporosis	> 2.5 SD below mean for age
Severe Osteoporosis	> 2.5 SD below mean for age and one or more fragility fracture

** World Health Organization: Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: Report of a WHO Study Group. World Health Organ Tech RepSer 1994; 843:1-129.*

In general, individual or raw measurements for a patient are of little value except as compared with these control values. The typical DEXA analysis therefore reports a Z score, which is the number of standard deviations (SDs) that a patient's BMD is above or below the mean value for persons of the patient's age and sex. The *T* score is the number of SDs the patient's BMD is either above or below the mean value for young adults of the same gender (Fig. 2) ***(Kaufman 1999).***

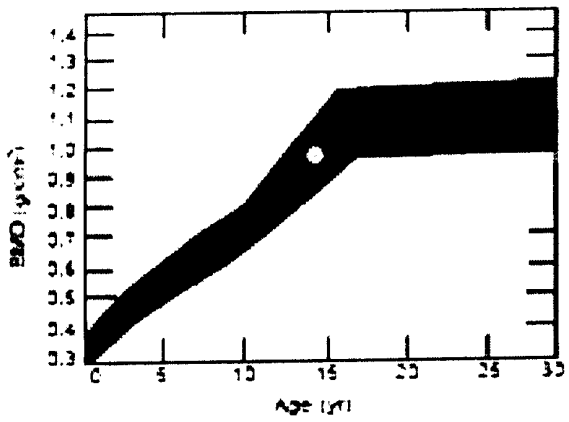


Figure 2:

-BMD of the lumbar spine in a healthy 14-year-old girl.

-Reference database of lumbar spine BMD as a function of age.

-The dark middle line is the mean BMD, the shaded dark and light sections represent 1 SD above and below the mean, respectively, the circle indicates the patient's BMD of 0.980 gm / cm^2 (the mean for spinal levels L1-L4).

(Tortolani et al., 2002)

Normative data for neonates and younger children are somewhat limited, and some authors question the validity of DEXA analysis for younger children, however, Koo et al ***(Koo et al., 1995)*** and Ellis et al ***(Ellis et al., 1994)*** have validated its accuracy and precision in infants and children.

In contrast to single photon absorptiometry, which permits analysis of the appendicular skeleton only, DEXA is able to measure both appendicular and axial bone mineralization ***(Cummings et al., 1993)***.

The radiation exposure is approximately 5 mrem per scan (the exposure from a typical chest radiograph is 25 mrem), and the test takes approximately 20 minutes to complete. Because bone strength and resistance to fracture depend not only on the amount of mineral present but also on the three - dimensional conformation, some investigators have questioned the accuracy of BMD measurements in predicting fracture risk ***(Martens et al., 1981)***. Despite this theoretic limitation, DEXA remains a powerful modality for documenting developmental changes in BMD, and responses to therapeutic interventions and its measurements have been shown to correlate well with fracture risk in adult patients ***(Cummings et al., 1993).***

Quantitative computed tomography (QCT) provides true three dimensional BMD measurements and is unique in that it can isolate the area of

interest from surrounding tissues. A purely trabecular area of a vertebral body can be isolated from the posterior elements, which may be involved with other processes, such as degenerative arthritis ***(Bauer et al., 1995)***.

QCT is available with most CT scanners, but the radiation dose is approximately 10 times that of DEXA and the tests are more costly and time consuming. Recent reports have suggested that quantitative ultrasound and magnetic resonance imaging (MRI) may accurately discriminate normal from osteopenic bone without exposing the patient to ionizing radiation ***(Hong et al., 2000, Bauer et al., 1995 & Jaworski et al., 1995)***.

In addition, these modalities may provide additional data, such as trabecular thickness and other micro-architectural factors that cannot be provided by DEXA. Despite these potential benefits of quantitative ultrasound and MRI, population-derived norms have not been generated for these modalities, and documentation of their accuracy, especially in young children (younger than 6 years old), is lacking. Neither quantitative ultrasound nor MRI currently is used as a screening tool for low BMD ***(Hong et al., 2000)***.

Use of variable SDs in pediatric reference ranges provide more accurate Z-scores and improved assessment of skeletal health. Total body BMD excluding the skull may provide a more sensitive indication of skeletal status and greater sensitivity to small BMD changes in pediatric subjects ***(Kaufman 1999).***

Osteopenia and Fracture Risk in the General Pediatric Population:

The liability to fracture is a function of trauma sustained and bone strength. Bone strength depends on both the density (quantity) of the bone and on the quality of the bone ***(Tortolani et al., 2002)***.

Bone mass and bone strength can be assessed by BMD. BMD is a primary predictor of fracture risk, with each SD decrease in BMD being associated with at least a 2-fold increase in the risk of fracture ***(Marshall et al., 1996).***

The BMD–fracture relationship generally applies across the skeleton, with some site-specificity; that is, hip fracture risk is more related to BMD measurements at the hip than lumbar spine or forearm ***(Melton et al., 1993).***

Fractures account for 25% of all pediatric injuries; the peak incidence of fractures in girls and boys occurs at 11 and 13 years of age, respectively ***(Landin 1997 & Hagino et al., 1990).*** These age peaks typically are attributed to risk-taking behavior, but recent work suggests that osteopenia that occurs during development may predispose children to fractures at specific skeletal locations. Results from a population- based study of children demonstrated differing rates of increase of BMD at the metaphysis and the diaphysis of the forearm ***(Bailey 1997 & Hagino et al., 1990).***

In particular, the ratio of metaphyseal to diaphyseal BMD is lowest in 11-year-old girls and in boys aged 12 to 13 years. These age ranges parallel the ages at which the highest rate of distal radius fractures occurs. Therefore, the authors concluded that low BMD at the distal metaphysis may contribute to distal radius fractures during adolescence. Similarly; girls aged 13 to 15 years with a history of a distal radius fracture are significantly more likely to have osteopenia than are fracture-free children ***(Bailey 1997).***

In a study of 100 affected children and 100 fracture-free children, DEXA was used to analyze BMD at the lumbar spine, ultra-distal radius, radius, hip trochanter, and total body. These findings identify the adolescent growth period as a critical period for bone mineralization and suggest that transient long bone weakness and increased fracture risk may follow PHV in boys and girls ***(Goulding et al., 1998)***.

Peak bone density attained during childhood may be a critical determinant of risk of fracture in adulthood. For this reason it is important to fully understand the factors influencing peak bone mineral density in children. These include diet, physical activity, growth, and genetic predisposition ***(Michaelsson et al., 1995, Valimaki et al., 1994, Johnston et al., 1992, Tylavsky et al., 1992, Gordon et al., 1991, Prince et al., 1991, Slemenda et al., 1991& Glastre et al., 1990).*** Some chronic diseases have also been reported to be associated with reduced peak bone mass in children ***(König et al., 1993 & Albanese et al., 1990).***

To date, no studies have investigated whether the gene-specific alterations in mineralization manifest clinically as increased fracture rates; however, the implications of these genetic alterations are important both for evaluation and treatment of children presenting with fractures. Further research will enable physicians to identify a subgroup of children at risk and provide novel therapies both to optimize bone mineral accrual during childhood and possibly to reduce fracture risk ***(Liu et al., 2003)***.

As previously mentioned, low bone mineral density at age 11 in girls and age 13 in boys represents a developmental phenomenon for which treatment is not currently available. Although the increased rate of fracture in children at these ages often has been attributed to risk-taking behavior, clearly some children at this age also have deficient calcium intake ***(Chan 1991).***

Calcium supplementation, either through dietary sources or vitamins, is recommended for children with three or more fractures in 1 year or a DEXA measurement of < 2.0 SDs. DEXA is currently recommended for healthy children who sustain three or more fractures in 1 year from low-energy mechanisms such as falls and sports. Children with a *Z* score of >2 SDs below the mean and a history of poor calcium intake or generally poor nutrition should be given calcium supplementation ***(Tortolani et al., 2002).***

Repeat DEXA scans are not necessary unless the child continues to sustain fractures or the clinician suspects a different diagnosis, such as osteogenesis imperfecta (OI) or idiopathic juvenile osteoporosis (IJO), where further reductions in bone mineralization could alter medical management ***(Tortolani et al., 2002)***.

Osteopenia and Osteoporosis in Childhood Disorders:

A -Idiopathic Juvenile Osteoporosis (IJO):

Some children with reduced BMD have genetic, hematologic, or metabolic defects that can be identified by thorough clinical examination. However, in a subset of otherwise healthy children, severe bone mineral loss for which there is no known cause develops between the ages of 4 and 16 years. Remarkably, this rare syndrome, IJO, reverses itself completely in virtually every case ***(Tortolani et al., 2002)***.

***CLINICAL PICTURE:*

Clinically, IJO is characterized by five cardinal features: onset before puberty, multiple fractures, pain in the back and the extremities, radiographic evidence of osteoporosis in new bone, and metaphyseal compression fractures. Children typically present with an insidious onset of pain in the back and legs. The physical examination is normal, with the exception of bone tenderness***(Chan 1991)***.

Severely affected children may have a mild kyphosis or pectus carinatum. All serum biochemical measurements are normal, and radiographs are notable for severe osteopenia with lower extremity metaphyseal impaction fractures. The distal tibia is particularly susceptible, and the vertebrae may be collapsed or wedged ***(Tortolani et al., 2002)***.

The clinician also must consider the diagnosis of leukemia in otherwise healthy children presenting with diffuse, symmetric osteopenia and bone tenderness, because these are common presenting signs. Presence of anaemia, fever or bleeding tendencies is suggestive of leukemia, and a peripheral blood smear helps to confirm the diagnosis ***(Chan 1991)***.

**CAUSE OF IJO:*

The cause of IJO is unknown; however, several mechanisms have been theorized. The reversibility of this disease at puberty suggests prepubertal hormone deficiency as a possible pathophysiologic mechanism ***(Tortolani et al., 2002)***.

In addition, qualitative abnormalities in type I collagen have been observed in a subset of patients with IJO, suggesting a possible relationship to OI ***(Pocock et al., 1995)***. Additional research likely will reveal multiple underlying mechanisms for IJO; currently, cases cannot be differentiated based on their clinical characteristics alone ***(Tortolani et al., 2002)***.

** *MANAGEMENT OF IJO:*

Supportive care is the most important treatment for IJO, children and their families should be reassured that the symptoms will remit during puberty.

- Physical activity should be curtailed to reduce fracture risk.

- Children must be examined by their physicians every 6 months to monitor pain and osseous deformity of both spine and lower extremities.

- Bracing may be considered for children with kyphosis and back pain.

(Tortolani et al., 2002)

B - Osteogenesis Imperfecta (OI):

OI is the most common genetic disease of the skeleton, affecting between 15,000 and 20,000 patients in the United States. Mutations in the synthesis of type I collagen lead to reduced BMD, skeletal fragility, and chronic pain. These symptoms are characteristic of this disease, which is marked by tremendous clinical heterogeneity. Orthopaedic surgeons play a central role in the management of these patients because osseous manifestations such as fractures, long bone deformity, and growth retardation are common ***(Tortolani et al., 2002)***.

Severe cases of OI are usually readily diagnosed; the four-types classification scheme of Sillence is often used to classify OI by clinical, radiographic, and genetic factors ***(Sillence et al., 1979),*** recently OI can be classified into eight types ***(Osteogenesis Imperfecta Foundation 2007)***.

Type I OI is the most common phenotype, and subtle manifestations may be overlooked. Type I OI accounts for approximately 60% of all cases and is the least severe form of the disease. It is transmitted as an autosomal dominant disorder. Children with type I OI have reduced bone volume, but because the bone is qualitatively normal, the phenotypic expression of the disease is mild. Compared to children with severe OI, children with type I OI have fewer fractures, less severe osteopenia, and little or no skeletal deformity, although heterogeneity exists within this phenotype ***(Tortolani et al., 2002)***.

Some children with type I OI experience frequent fractures in infancy, with the rate decreasing during adolescence. Others have milder disease that is not manifest until adulthood, when unexplained osteopenia occurs. A child who presents to the emergency department with a new fracture should be examined for the presence of blue sclerae because this feature is present in almost all cases of type I OI ***(McCarthy and Frassica 1998)***.

A family member with a history of multiple fractures also is an indicator for this diagnosis. However, almost 20% to 30% of patients have apparently normal parents and so may represent new mutations. Approximately 25% of patients with type I OI have hearing impairments, and dentinogenesis imperfecta occurs in a subset of these patients as well ***(McCarthy and Frassica 1998).***

Importantly, because osteopenia may not be profound and skeletal deformity may be absent, normal radiographic examination does not rule out type I OI (Fig. 3) ***(Tortolani et al 2002)***

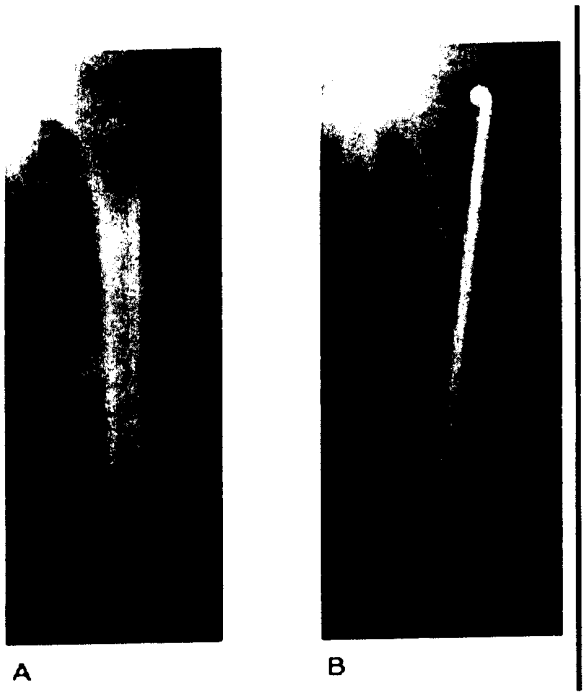


Figure 3:

AP radiographs of the femur of an 8-years old patient with OI. Osteopenia is not obvious (A); however, this patient had a fracture treated by intramedullary fixation (B) ***(Tortolani et al 2002)***

DEXA may aid in the diagnosis of OI when clinical and radiographic evidence is lacking. Healthy children who sustain three or more low energy fractures over a 1-year period should have DEXA as part of the workup for OI. Children with type I OI have been shown to have significantly reduced BMD in

the femoral neck compared with age- and weight-matched healthy children ***(Davie and Haddaway 1994).***

It has been postulated that patients with OI have deficiencies in mineralization secondary to the abnormalities in type I collagen synthesis. Biochemical studies suggest that increased bone resorption and a reduced rate of osteogenesis also play a role ***(Brenner et al., 1994).***

In support of this, bisphosphonates, which are potent inhibitors of bone resorption, have been found to lead to increased BMD and reduced fracture rates in children with OI. Although bisphosphonates currently are not approved by the US Food and Drug Administration for use in children, their use in some children with OI and neuromuscular disorders appears to be efficacious ***(Glorieux et al., 1998 & Brumsen et al., 1997).***

Type II OI can be further subclassified into groups A, B, C, which are distinguished by radiographic evaluation of the long bones and ribs. Type IIA; demonstrates broad and short long bones with broad and beaded ribs. Type IIB; demonstrates broad and short long bones with thin ribs that have little or no beading. Type IIC; demonstrates thin and longer long bones with thin and beaded ribs ***(Tortolani et al 2002).***

Collagen is not of a sufficient quality or quantity; most cases die within the first year of life due to respiratory failure or intracerebral hemorrhage, there is

severe respiratory problems due to underdeveloped lungs and severe bone deformity and small stature ***(Barnes et al., 2006).***

Type III is distinguished among the other classifications as being the "Progressive Deforming" type, wherein a neonate presents with mild symptoms at birth and develops the aforementioned symptoms throughout life. Collagen quantity is sufficient but is not of a high enough quality which is presented by easily bones fractures, sometimes even before birth, severe bone deformity, short stature, spinal curvature and sometimes barrel-shaped rib cage, loose joints, poor muscle tone in arms and legs, discolouration of the sclera (whites of the eyes) and sometimes early loss of hearing ***(Byers et al., 2006).***

Type IV can be further subclassified into types IVA and IVB characterized by absence (IVA) or presence (IVB) of dentinogenesis imperfecta. Collagen quantity is sufficient but is not of a high enough quality presented by easily bones fractures, especially before puberty, Short stature, spinal curvature and barrel-shaped rib cage, bone deformity which is mild to moderate and early loss of hearing ***(Johnson et al., 2002)***.

Type V has the same clinical features as Type IV; distinguished histologically by "mesh-like" bone appearance. Further characterized by the "V Triad" consisting of a) radio-opaque band adjacent to growth plates, b) hypertrophic calluses at fracture sites, and c) calcification of the radio-ulnar

interosseous membrane. At the present time, the cause for Type V is unknown, though doctors have determined that it is inherited ***(Glorieux et al., 2000).***

Type VI has the same clinical features as Type IV; distinguished histologically by "fish-scale" bone appearance ***(Glorieux et al., 2002).***

Ward et al. described a novel form of autosomal recessive OI, which they designated OI type VII, in 8 affected individuals in a small consanguineous First Nations community in northern Quebec ***(Ward et al., 2002 & Morello et al., 2006).***

Cabral et al. described a form of autosomal recessive OI, which they designated OI type VIII, characterized by white sclerae, severe growth deficiency, extreme skeletal undermineralization, and bulbous metaphyses ***(Cabral et al., 2007).***

C - Rickets and Osteomalacia:

Rickets is a pediatric disorder characterized by deformity and growth retardation caused by defective mineralization of the growth plate. Osteomalacia is defective mineralization of osteoid; because osteoid is remodeled throughout life, this condition occurs in both children and adults ***(Tortolani et al., 2002).***

Many causes of rickets and osteomalacia have been identified (Table 6); however, the central theme is inadequate calcium or phosphate for normal skeletal mineralization.

Table 6: Causes of Rickets and Osteomalacia in Children

Vitamin D deficiency ▪ Inadequate sun exposure. ▪ Low dietary intake.
Gastrointestinal Causes ▪ Following a Polya or Billroth II gastrectomy ▪ Abnormal fat metabolism ▪ Diffuse injury to the wall of small bowel, as occurs with inflammatory processes such as celiac disease, Crohn disease, or disorders associated with a short loop (shunts or fistulae) or rapid transit (gluten-sensitive enteropathy and other sprue-like syndromes);
Congenital diseases ▪ Vitamin D-dependnt rickets,type I (failure of conversion of 25-hydroxyvit D to 1,25-dihydroxyvit D) ▪ Vitamin D-dependnt rickets,type II (end-organ insensitivity to autogenous 1,25-dihydroxyvitamin D) ▪ X- linked hypophosphatemic rickets (Vit D resistant rickets)
Oncogenic Osteomalacia Soft tissue and bone tumours
Idiopathic hypophosphatemic rickets (high 1,25 vit D levels & hyperabsorption of Ca)
Vitamin D metabolism abnormalities ▪ Renal Failure ▪ Renal Osteodystrophy ▪ Renal Tubular Acidosis ▪ Phenytoin therapy

(Tortolani et al., 2002)

In addition to the pathognomonic widening of the physeal plate and cupping of the metaphysis, generalized osteopenia may be profound and demonstrable by radiographs alone (Fig. 4).

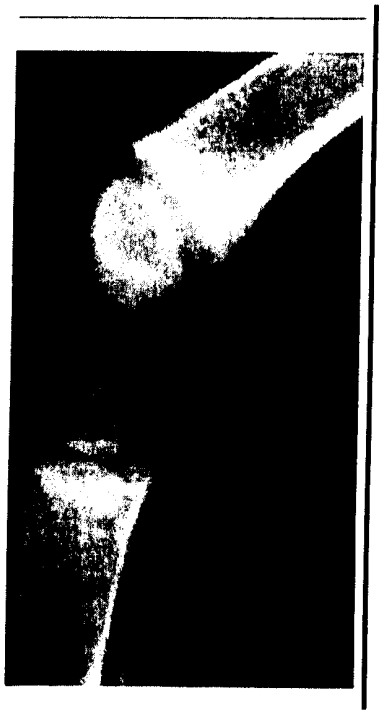


Figure 4:

-Lateral radiograph of the knee of a 6-year-old patient with rickets.
-Diffuse osteopenia is present in the metaphysis, with widening of the physeal plate and metaphyseal cupping.
(Tortolani et al., 2002)

Children with dark skin pigmentation, those who have been breast-fed exclusively without additional vitamin D supplementation, those who live in northern cities, those consuming a strict vegetarian diet, and those whose mothers lacked calcium and vitamin D supplementation during pregnancy are particularly susceptible. Vitamin D-dependent rickets is a continuing problem in North America ***(Binet and Kooh 1996, Sills et al., 1994 & Bhowmick et al., 1991)***.

Highly pigmented children of Asian and African immigrants should be evaluated carefully because the prevalence of vitamin D-dependent rickets approaches 40% in parts of these continents ***(Karrar 1998).*** Bowing of the lower extremities with shortening of the long bones and spinal kyphosis are the most common presenting signs in patients with vitamin D-dependent rickets; however, fractures often complicate the disease (Fig. 5).

Repeated clavicle fractures in infants below height and weight norms should alert the physician to the possibility of rickets. In addition, stress fractures may be present in 20% of affected children ***(Herman and Bulthuis 1999)***.

Figure 5:

AP radiograph of the left knee and lower leg of a 7-year-old patient with rickets.
Metaphyseal cupping and widened physes can be recognized.
Note the pathologic fracture in the distal tibia and fibula.
(Tortolani et al., 2002)

Genetically caused rickets also is seen. One example, type I vitamin D-dependent rickets, has been well characterized as a defect in the 1- alpha hydroxylase enzyme, which converts 25(OH) vitamin D to 1,25(OH)2 vitamin D, the biologically active form. Type II vitamin D-dependent rickets is caused by mutations in the vitamin D receptor ***(Tortolani et al., 2002)***.

More than 10 mutations in the vitamin D receptor have been characterized, all of which are manifested as severe rickets. The profound physiologic effects of rickets-inducing vitamin D receptor mutations are in sharp contrast to findings in the studies which showed that allelic variation at the vitamin D receptor locus results in only subtle phenotypic manifestations of reduced BMD ***(Sainz et al., 1997 & Morrison et al., 1994).*** Further investigation is warranted to elucidate more clearly the molecular structure of the vitamin D receptor gene and its associated regulatory domains to explain this apparent dichotomy.

The key task for most orthopaedic surgeons is to identify patients at risk for rickets and to establish the diagnosis. Orthopaedic surgeons should feel comfortable initiating the work-up for this disease by ordering and interpreting the results of serum calcium, phosphate, vitamin D, and alkaline phosphatase tests prior to referral to a pediatric endocrinologist ***(Tortolani et al., 2002)***.

Nutritional rickets responds in dramatic fashion to vitamin D supplementation, and all exclusively breast-fed infants should receive oral supplementation with 400 IU of vitamin D daily and/or increased sunlight or ultraviolet light exposure. For infants, exposure to 30 min of sunlight per week in the summer while wearing only a diaper, or 120 min per week while fully clothed with the head exposed, is sufficient ***(Specker et al., 1985).***

Metabolic control of this disorder is necessary before considering corrective osteotomy for angular deformity in these children. Furthermore, prompt recognition and appropriate treatment of vitamin D deficiency enables these patients to reach their peak bone mineral status before entering adulthood ***(Tortolani et al., 2002)***.

D - Juvenile Arthritis:

Juvenile rheumatoid arthritis (JRA) is associated with poor linear growth, increased fracture rates, and reduced bone mineralization.

A decrease in BMD has been demonstrated in almost 60% of children with juvenile chronic JRA, and limitation of function has been correlated with reduced BMD in these patients ***(Pereira et al., 1998).***

Although all skeletal sites may be involved, the appendicular skeleton appears to be more dramatically affected. The severity of the condition is the most critical factor influencing BMD in children with JRA. Although global reduction in bone turnover is apparent, reduced bone formation by osteoblasts is most likely

the primary physiologic defect. Prepubertal patients presenting with chronic arthritis should be followed closely because JRA interrupts the normal hormonal signals that enhance skeletal mineralization during this period of development ***(Tortolani et al., 2002)***.

Corticosteroid use accelerates BMD loss in children with chronic arthritis. The exact mechanisms of corticosteroid action are unknown, and therefore pharmacologic blockade of this effect is not currently possible.

The degree to which corticosteroids impact bone mineralization depends both on cumulative dose and skeletal location. Vertebral collapse is more common in children receiving a cumulative dose of at least 5 g ***(Varonos et al., 1987)***.

Trabecular bone in the lumbar spine is most sensitive to corticosteroids ***(Pereira et al., 1998).*** Osteopenia should be suspected in all children presenting with chronic arthritis. The severity of the disease and the cumulative dose of steroids should alert the physician to the possibility of profound reductions in BMD (Fig. 6).

Other factors, such as poor calcium and vitamin D intake and inadequate exercise, also may exacerbate the degree of osteopenia.Orthopaedic surgeons need to be aware of these factors so that, in addition to managing osseous manifestations of the disease, they can educate their patients and identify children in high-risk groups ***(Tortolani et al., 2002)***.

Figure 6:

AP radiograph of the pelvis of a 13-years old patient with JRA.

-Note the profound deficiency of bone mineralization of the proximal femora as well as hip arthritis. ***(Tortolani et al., 2002)***

E - Neuromuscular Disorders:

Cerebral palsy and myelomeningocele are the most common neuromuscular disorders. Profound osteoporosis develops in many of affected children. This loss of BMD leads to pain, additional disability, and, ultimately, pathologic fractures. Inability to ambulate in general and prolonged immobilization after surgical procedures in particular are thought to explain much of the dramatically reduced BMD and increased risk of pathologic fractures in these patients ***(Tortolani et al., 2002)***.

In one retrospective cohort study, fractures developed in the lower extremity in 29% of children within the 3 months following spica cast removal. The treatment of these fractures and associated complications are costly aspects of the medical care of these patients ***(Sturm et al., 1993)***.

DEXA has enabled the identification of multiple factors that lead to defects in bone mineralization in children with cerebral palsy. Although the inability to ambulate correlates most strongly with low BMD, low calcium intake, nutritional status, immobilization, and pattern of involvement are additional contributing factors ***(Henderson et al., 1995).***

Prematurity and anticonvulsant use also may contribute to mineralization defects in these children. A histomorphometric data from pediatric patients with neuromuscular disorders revealed severe bone loss in virtually every patient ***(Buch et al., 1998)*** (Fig. 7).

Severe metabolic bone disease may be obvious in severely affected patients; however, orthopaedic surgeons must be aware of this risk even in highly functioning patients or patients in the early stages of the disease.

Management of cerebral palsy and other neuromuscular disorders requires a multidisciplinary team approach with the orthopaedic surgeon occupying a

central role. Limiting immobilization by combining surgical procedures, optimizing nutritional status, and maintaining calcium supplementation all have the potential to increase BMD during the childhood years. Preliminary use of bisphosphonates shows promise for reducing mineral loss in patients with neuromuscular disorders ***(Brumsen et al., 1997).***

Figure 7:

-Low-power photomicrograph of undecalcified bone from the calcaneus of a patient with myelomeningocele showing severe osteopenia.

-Trabeculae are reduced to small, unconnected buttons (arrows). ***(Tortolani et al., 2002)***

CHAPTER III

ENVIRONMENTAL TOBACCO SMOKE

Environmental tobacco smoke (ETS) is the smoke present in the air that nonsmokers inhale, inhalation of ETS is referred to as 'passive smoking' or 'involuntary smoking'. Exposure to environmental tobacco smoke (ETS) has recently been classified as class I carcinogen by the International Agency for Research on Cancer ***(International Agency for Research on Cancer (IARC) 2004).***

Since the mid-1980s there has been increasing interest in the effects of passive smoking on the health of children. As children spend much of their early life in the presence of their parents, children who have parents that smoke will have a prolonged and close exposure to environmental tobacco smoke ***(Working Party of the Royal College of Physicians 1992 & Poswillo and Alberman 1992)***.

Although passive smoking is a well-known health hazard in children, there are very few reports addressing the problem of smoking by fathers only, as opposed to both parents ***(Dietrich et al., 2003)***.

Exposure to environmental tobacco smoke (ETS), both pre- and postnatal, is an important and well-known health hazard to children ***(Dietrich et al., 2003, International Agency for Research on Cancer (IARC) 2002 & Jones et al., 2002).***

The World Health Organization has estimated that ~700 million, or almost half of the children in the world, are exposed to ETS. This exposure occurs primarily in the home, although cigarette-consumption level and children's exposure outside the home; in other enclosed surroundings, for example in a motor vehicle, must also be considered. In their homes, children depend on parents' good will and capacity to minimize their ETS exposure ***(World Health Organization, Division of Noncommunicable Diseases, Tobacco Free Initiative 1999).***

Some experts believe that self-reports on smoking status may not be reliable, or the range of uptake in passive smokers may be affected by various factors ***(Ilikali et al., 2001)***. Other studies, however, have demonstrated that parent-reported children's exposure to ETS is significantly correlated to objective tests and is therefore valid and reliable ***(Emerson et al., 1995).***

Most smoking parents make efforts to protect their children. However, nobody can tell how meaningful different modes of action might be. In exceptional cases, as reported recently, a child can still be massively exposed to ETS in the home ***(Johansson et al., 2003)***.

Children's exposure to tobacco constituents during fetal development and via environmental tobacco smoke (ETS) exposure is perhaps the most hazardous of children's environmental exposures. A large literature links both prenatal maternal smoking and children's ETS exposure to decreased lung growth and increased rates of respiratory tract infections, otitis media, and childhood asthma, with the severity of these problems increasing with increased exposure ***(Stazi et al., 2002, Mannino et al., 2001& DiFranza and Lew 1996).***

Sudden infant death syndrome, behavioral problems, neurocognitive decrements, and increased rates of adolescent smoking also are associated with such exposures (Table 7). Studies of each of these problems suggest independent effects of both pre- and postnatal exposure for each, with the respiratory risk associated with parental smoking seeming to be greatest during fetal development and the first several years of life ***(DiFranza et al., 2004).***

The effect of maternal smoking during pregnancy on children's birth weight has been recognized since 1957 ***(Simpson 1957),*** and the first report concerning the adverse effects of environmental tobacco smoke (ETS) on children's health was published in 1967 ***(Cameron 1967).*** Since that time, >150 studies of the effects of ETS on respiratory illness in children alone have been published ***(Jinot and Bayard 1996).***

Table 7: Health Effects Associated With Exposure to Environmental Tobacco Smoke**

Effects Causally Associated with ETS Exposure

1-Developmental Effects
- Fetal Growth: Low birth weight or small for gestational age
- Sudden Infant Death Syndrome (SIDS)

2-Respiratory Effects
- Acute lower respiratory tract infections in children (*e.g.*, bronchitis and pneumonia)
- Asthma induction and exacerbation in children
- Chronic respiratory symptoms in children
- Eye and nasal irritation in adults
- Middle ear infections in children

3-Carcinogenic Effects
- Lung Cancer
- Nasal Sinus Cancer

4-Cardiovascular Effects
- Heart disease mortality
- Acute and chronic coronary heart disease morbidity

Effects with Suggestive Evidence of a Causal Association with ETS Exposure

1-Developmental Effects
- Spontaneous abortion
- Adverse impact on cognition and behavior

2-Respiratory Effects
- Exacerbation of cystic fibrosis
- Decreased pulmonary function

3-Carcinogenic Effects
- Cervical cancer

***California Environmental Protection Agency, Health Effects of Exposure toEnvironmental Tobacco Smoke; Final Report September 1997*

A similarly large, although generally newer body of work, clearly links both prenatal maternal smoking and ETS exposure to ear infections, sudden infant death syndrome (SIDS), behavioral problems, and neurocognitive deficits. Aligne and Stoddard estimated the annual excess in deaths in children younger than 5 years as a result of tobacco smoke exposure at close to 6000, exceeding deaths as a result of all injuries combined ***(Aligne and Stoddard 1997)***.

Exposure of children to ETS in the home increases the incidence of middle ear disease, asthma, wheeze, cough, phlegm production, bronchitis, bronchiolitis, pneumonia, and impaired pulmonary function, and it has also been associated with snoring ***(Corbo et al., 1989)***, adenoid hypertrophy ***(Huang and Giannoni 2001)***, tonsillitis, and sore throats ***(Willatt 1996).***

In 4 of 5 studies, the incidence of tonsillectomy was doubled for children who live in households with smokers ***(Hinton et al., 1993, Stahlberg et al., 1986 & Said et al., 1978).*** Maternal smoking is associated with an increased incidence of wheezing illness up to 6 years of age with an odds ratio of 1.31 ***(Strachan and Cook (I)1998).***

Characteristics of Environmental Tobacco Smoke (ETS)

Passive smoking is defined as an involuntary environmental exposure to cigarette side-stream smoke plus exhaled smoke from smokers. ETS is composed of more than 3800 chemical compounds ***(Etzel 2001).***

It consists of a diluted combination of **sidestream tobacco smoke (SS),** which is the smoke, emitted from the lit end of a cigarette, cigar or pipe, as well as **exhaled mainstream smoke (MS),** which is the smoke that emerges from the mouth of the smoker.

Sidestream smoke represents the major source for ETS, side-stream smoke is a combination of gas and particulate matter that evolves from the smouldering end of the cigarette while the smoker is not puffing and consists of cytotoxic substances including polycyclic aromatic hydrocarbons, aromatic amines, and poisonous gas in quantities much higher than those found from cigarette mainstream smoke ***(Nelson 2001).***

The exhaled portions of MS and the vapor phase components that diffuse through the wrapper into the surrounding air constitute minor contributors to ETS.

ETS, SS and MS are complex mixtures of 3,800 substances, including more than 40 known or suspected carcinogenic compounds, between 300-400 of the 3,800 compounds in tobacco smoke have been quantitatively measured in SS and MS ***(Etzel 2001).***

ETS consists of solid respirable particulates (mean diameter = 0.32 ug), semivolatile, and volatile organic compounds (VOCs).

▼ Some of the compounds present in the vapor phase of MS and SS include (makes up about 85% of ETS): ***(Environmental Tobacco Smoke 1986)***

- *Nicotine*, which is a highly toxic alkaloid that is both a ganglionic stimulant and depressant.

- *Carbon monoxide* which is known to interfere with oxygen transport and utilization ***(Holbrook 1998).***

- *Carbon dioxide*
- *Benzene*
- *Toluene*
- *Formaldehyde*
- *Acrolein*
- *Acetone*
- *Hydrazine*
- *Ammonia*

▼ Some of the compounds present in the particulate phase of SS and MS include:

- *Anatabine*
- *Phenol*
- *Catechol*
- *Aniline*
- *Cadmium*
- *Nickel*
- *Zinc*

▼ Some compounds such as nicotine exist in both vapor and particulate phase.

ETS and Respiratory Tract Infection:

It has been suggested that parental smoking might be associated with respiratory infections in children because the parents themselves are more likely to bring home a respiratory infection. This mechanism would not explain why parental smoking increases the risk and severity of respiratory syncytial virus bronchiolitis in infants ***(Breese-Hall et al., 1984 & Pullan and Hey 1982).***

Even when controlling for parental symptoms, birth weight, and family size, bronchitis and pneumonia are more common during the first year of life in smoking households ***(Colley and Holland 1974 & Harlap and Davies 1974).*** Parental symptoms do not account for the increased incidence of cough among children of smokers ***(Dodge 1982 & Bland et al., 1973).***

In smoking households, children are at greater risk of hospitalization for respiratory illness ***(Anderson et al., 1988 & Chen et al., 1986).*** A meta-analysis concluded that ETS was associated with an approximate doubling of the risk of lower respiratory tract infection in children, with the risk declining after the age of 2 ***(Li et al., 1999).***

Smoking during pregnancy seems to add an additional risk to that associated with postnatal exposure to ETS ***(Jedrychowski and Flak 1997).*** Maternal smoking during pregnancy has been associated with an odds ratio of 3.8 for infant death as a result of respiratory disease (excluding conditions related to prematurity) ***(Malloy et al., 1988).***

ETS and Asthma:

ETS increases both the prevalence and the severity of asthma ***(Strachan and Cook (II) 1998).*** Several authors have argued that the evidence regarding ETS and asthma is strong enough to conclude that the relation is causal, although the mechanism has not been established ***(Cook and Strachan 1997, DiFranza and Lew 1996 & US Environmental Protection Agency 1992).***

In a meta-analysis, the risk of developing asthma was 1.37 if either parent smoked ***(Strachan and Cook (II) 1998).*** Household smoking increases the frequency of attacks ***(Strachan and Carey 1995),*** the number of emergency department visits ***(Evans et al., 1987),*** and the risk of intubation ***(Leson and Gershwin 1995).***

The relationship between parental smoking and asthma has stood up when controlled for a long list of potential confounders, including gender, age, urbanization, education, crowding, dampness, mold, cooking fuel, parental respiratory symptoms, parental asthma, and the child's smoking ***(Agabiti et al., 1999, Martinez et al., 1992 & Weitzman et al., 1990).***

Strong indicator that the association is not attributable to unmeasured confounders is reports that asthma severity has improved in children when exposure was reduced ***(O'Connell and Logan 1974).***

Several authoritative reviews have concluded that parental smoking has adverse effects on pulmonary function in children ***(National Cancer Institute 1999, US Environmental Protection Agency 1992 & US Department of Health and Human Services 1986).***

Meta-analysis of 21 studies found a reduction in forced expiratory volume in 1 second of 1.4%, midexpiratory flow rate of 5%, and end expiratory flow rates of 4.3% ***(Cook et al., 1998).*** It is likely that some of this effect is attributable to in utero exposure as smoking during pregnancy has adverse effects on pulmonary function measured in the neonatal period ***(Stick et al., 1996)***.

Postnatal ETS exposure has been associated with small declines in pulmonary function as well, but the mechanism of damage has not been identified ***(Chen et al., 1986).***

ETS and Otitis Media (OM):

The epidemiologic data regarding a possible link between ETS and otitis media (OM) has been reviewed several times by federal agencies; the Surgeon General, the National Research Council ***(National Research Council, Committee on Passive Smoking 1986),*** the US Environmental Protection Agency (EPA) (***US Environmental Protection Agency 1992***), and the National Cancer Institute (NCI)/California EPA ***(National Cancer Institute 1999).***

The NCI report concluded that "overall, the epidemiologic data strongly support a relationship between ETS exposure in the home and either acute OM or OM with effusion, particularly among children under 2 years of age." In addition, a thorough peer-reviewed, systematic, quantitative meta-analysis of 11 papers on acute OM, 9 on recurrent OM, 5 on middle ear effusion, and 9 on surgery for OM with effusion was published in 1998. It concluded, "There is likely to be a causal relationship between parental smoking and both acute and chronic middle ear disease in children." ***(Strachan and Cook (I) 1998)***

Three additional papers with strong designs for investigating the ETS—OM association have been published since 1997 ***(Ilicali et al., 2001, Stathis et al., 1999 & Adair-Bischoff and Sauve 1998)***. These 3 studies found relative risks ranging from 1.9 to 3.9. One study, used hair cotinine measurements, home visits, and inspection of physician medical records on a subset of the participants to validate the exposure and outcome information ***(Adair-Bischoff and Sauve 1998).***

The second study used an objective definition of both exposure and outcome, with ETS measurement by urine cotinine and OM assessment by direct examination by an ears, nose, and throat specialist ***(Ilicali et al., 2001).***

The third study, studied a large prospective cohort recruited before birth and found that prenatal smoking is more important than postnatal smoking with respect to OM risk ***(Stathis et al., 1999).***

ETS and sudden Infant Death Syndrome (SIDS):

SIDS is the leading cause of death of infants 1 month to 1 year of age in the United States. Multiple potential risk factors have been identified ***(National Cancer Institute 1999 & Dwyer and Ponsonby 1995).***

The incidence in developed countries has declined dramatically during the 1990s, after public health campaigns advising parents to place sleeping infants on their back. Now that fewer infants sleep prone, maternal smoking is the major suspected risk factor for SIDS ***(Mitchell 1999)***.

The epidemiologic data regarding a possible link between ETS and SIDS has been reviewed several times by federal agencies, as well as by the World Health Organization: the Surgeon General (***US Department of Health and Human Services. 1986)***, US EPA (***US Environmental Protection Agency 1992***), NCI/California EPA ***(National Cancer Institute 1999)***, and World Health Organization ***(World Health Organization 1999).*** The NCI report concluded that "existing data indicate a causal relationship between maternal smoking in general and SIDS." ***(National Cancer Institute 1999).***

In addition, a thorough, peer-reviewed, systematic, quantitative review of 39 studies, was published in the medical literature. It concluded that, "Maternal smoking doubles the risk of sudden infant death syndrome. The relationship is almost certainly causal. The epidemiologic evidence points to a causal relationship

between SIDS and postnatal exposure to environmental tobacco smoke." ***(Anderson and Cook 1997)***

The distinction between effects of prenatal versus postnatal exposure was believed to warrant additional investigation. Recent studies were conducted after the switch to supine sleeping and the resulting decline in SIDS deaths. Investigations that quantified smoking found a significant dose–response relation between smoking and SIDS ***(Wisborg et al., 2000, Dwyer et al., 1999 & l'Hoir et al., 1998).***

One study found that smoking cessation during pregnancy reduces the risk of SIDS ***(Alm et al., 1998)***. Bed-sharing (infant co-sleeping with the mother) seems to be a risk for SIDS only when the mother is smoker, even after controlling for alcohol use and other risk factors ***(Mitchell et al., 1997).***

It is difficult to distinguish the effect of active maternal smoking during pregnancy from that of postnatal ETS exposure of the infant. However, clear evidence for a non-maternal ETS effect arises from 6 studies that examined SIDS and paternal smoking in which the mother is a nonsmoker. The pooled unadjusted relative risk from these studies is 1.4 ***(World Health Organization 1999).*** A recent case-controlled study found differences in nicotine in the lungs of infants who died of SIDS and infants who died of other causes ***(McMartin et al., 2002).***

Effects of Maternal Smoking on Intrauterine Growth:

In 1957, Simpson reported an adverse effect of maternal smoking on birth weight ***(Simpson 1957)***. Subsequent studies have confirmed this finding and demonstrated a direct dose-response effect ***(MacArthur and Knox 1988, Kline et al., 1987, Kleinman and Madans 1985& MacMahon et al., 1965).***

The effect on birth weight is more attributable to intrauterine growth retardation than to preterm delivery. Kramer et al ***(Kramer et al., 1990)*** estimated the effect of prenatal maternal smoking as a 5% reduction in relative weight per pack of cigarettes smoked per day. Cigarette smoking is the single most important factor affecting birth weight in developed countries ***(Kramer 1987).***

Meyer and Comstock ***(Meyer and Comstock 1972)*** reported that the effect of maternal cigarette smoking on infant birth weight was an average reduction of 150 to >300 g. Maternal and paternal smoking both are associated with lower birth weight, with maternal smoking having a greater effect ***(Ramsay and Reynolds 2000 & Matsubara et al., 2000).***

A randomized controlled intervention study demonstrated that reduction of smoking during pregnancy improves the infant birth weight ***(Sexton and Hebel 1984).***

Pre-natal maternal smoking affects the fetus in a number of ways that may result in chronic hypoxia and low birth weight. Placental vascular resistance is

often increased when women smoke during pregnancy ***(Howard et al., 1987 & Lehtovirta and Forss 1978)***. Maternal smoking is associated with alterations of protein metabolism and enzyme activity in fetal cord blood ***(Jauniaux et al., 2001 & Ulm et al., 1995).***

Cigarette smoking during pregnancy transiently lowers maternal uterine blood flow and reduces flow of oxygen from the uterus to the placenta ***(Morrow et al., 1988)***. Increased levels of carboxyhemoglobin are found in both maternal and fetal blood when the mother smokes during pregnancy, and this can lead to fetal hypoxia ***(Soothill et al., 1996)*** and the fetus experiences chronic hypoxic stress, as evidenced by elevated hematocrit levels ***(Bush et al., 2000).***

Poor intrauterine growth has a lasting effect on subsequent growth ***(Haug et al., 2000)*** and development of children ***(Dunn et al., 1976)***, including an increased risk of emotional and behavioral problems ***(Breslau and Chilcoat 2000, McCarton 1998, Pharoah et al., 1994& Barros et al., 1992)***, and lowered cognitive abilities and hyperactivity ***(Breslau et al., 2000 & Johnson and Breslau 2000).*** A recent paper also indicated decrements in IQ associated with lower birth weight in children born with weight < 2500 g ***(Matte et al., 2001).***

In rats, in utero exposure to nicotine has been shown to have a teratologic effect on neuronal development in the brain. Prenatal exposure results in profound alterations in neurotransmitter disposition, which are evident in specific neuronal pathways and which persist after birth. Although nicotine has been the prime focus

of animal studies on this topic, tobacco smoke is composed of thousands of chemicals and the contributions of individual chemicals is unknown ***(Slotkin et al., 1987)***.

In humans, maternal smoking increases the likelihood for a child to be born with a small head circumference ***(Kallen 2000).*** Children who are born to smoking mothers experience catch-up growth in weight and partial catch-up growth in length, but the differences in head circumference persist to at least 5 years of age ***(Vik et al., 1996).*** No difference in head circumference measurements was found when women who are pregnant stop smoking before 32 weeks' gestation ***(Lindley et al., 2000).***

ETS and Behavior:

The impact of prenatal and postnatal exposure to tobacco smoke on human behavior and neurologic development has been reviewed in many recent articles ***(Weitzman et al., 2002, Wakschlag et al., 2002, Ernst et al., 2001& Eskenazi and Castorina 1999)*** The literature strongly suggests that such exposures lead to negative behavioral and neurocognitive effects in children ***(Johnson et al., 2000 & Naeye 1992).***

Studies of children whose mothers smoked during pregnancy have consistently demonstrated that such children have higher rates of behavior

problems than those not exposed. Olds ***(Olds 1997)*** noted that 10 of 11 human studies found increased rates of child behavior problems and attention-deficit/hyperactivity disorder–like behaviors even after controlling for many potential confounders. Follow-up in these studies has varied from the newborn period through adolescence ***(Wakschlag et al., 1997, Milberger et al., 1996 & Fergusson et al., 1993).***

Smoking and Bones:

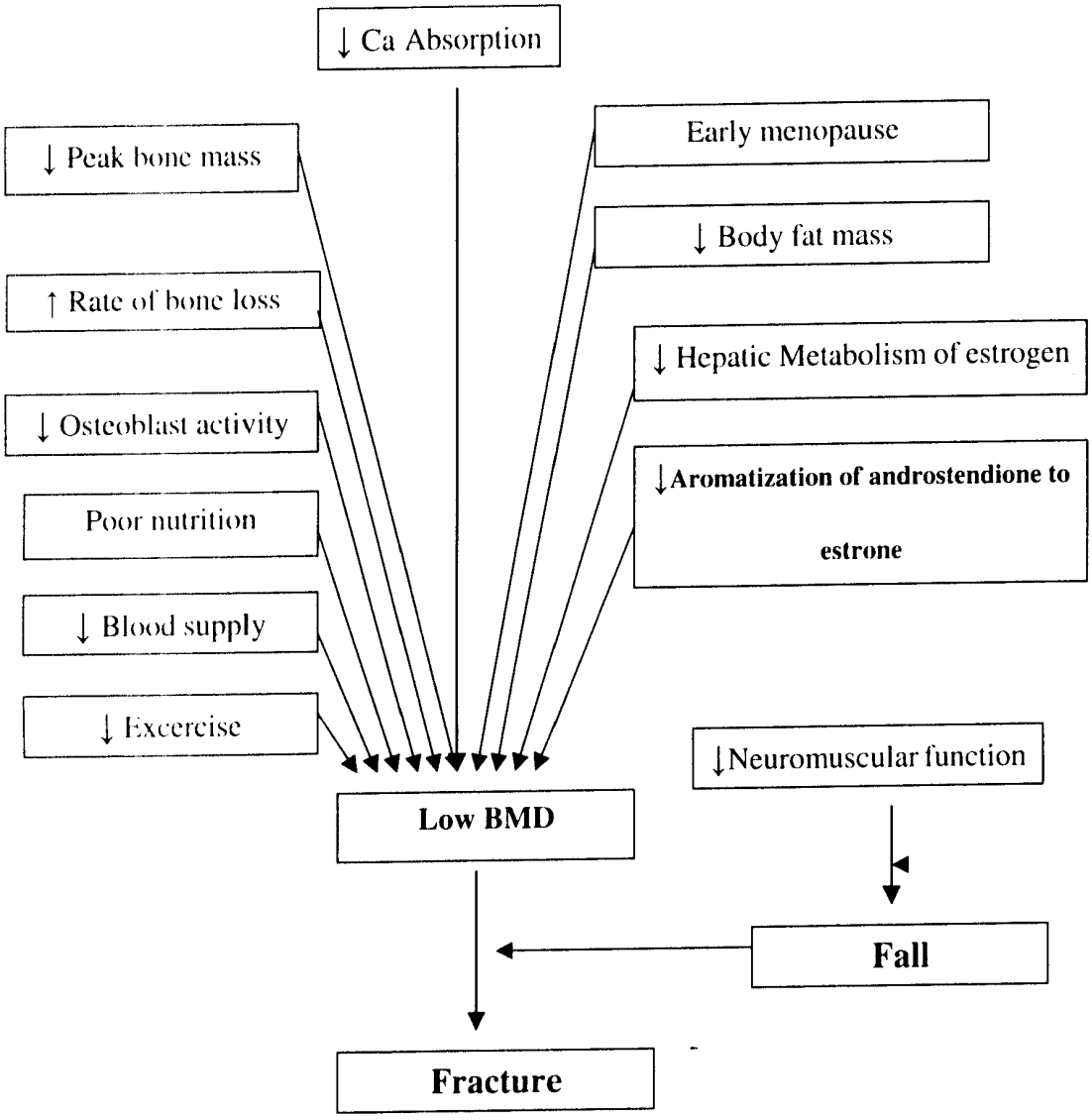
Bone is a dynamic tissue that is continuously remodeled throughout life by the processes of resorption, new formation, and mineralization. Physical forces (exercise, body weight) and hormonal factors (estrogen, testosterone) stimulate osteoclasts to begin the process of bone resorption. Osteoblasts then move into the resorption cavity and form new bone. Mineralization occurs more slowly during the next 3 to 4 months ***(Molly 1999)***.

Cigarette use has been postulated to exert an adverse effect on all three phases of the remodeling (Figure 8), but research to date has not clarified which, if any, of the thousands of breakdown products of burning cigarettes directly affects the osteoclasts and osteoblasts ***(Molly 1999 &Young et al., 1995)***.

A history of smoking results in fracture risk that is substantially greater than that explained by measurement of BMD ***(Kanis et al., 2005).***

Figure 8:

Possible mechanisms for effect of smoking on bone mass and fractures of children and adult ***(Molly 1999).***



Measuring exposure to smoke

Considerable work has been undertaken to identify ways of measuring the extent of tobacco smoke exposure in non-smokers, exposure depends on several factors:

- number of smokers in the enclosed area
- size and nature of area
- degree of ventilation

Due to these factors, a more reliable measure of human exposure is through body fluids like blood or urine versus respired air. ***(Environmental Tobacco Smoke 1986)***

Carbon monoxide in the blood (COHb) maybe useful for comparing degrees of smoke inhalation in acute exposures, BUT important to remember:

- carbon monoxide comes from other sources
- exhaled CO is not valid in indicating chronic exposure to ETS.
- measuring CO in the blood and respired air probably not the best measure for human exposure to ETS

Nicotine and Cotinine in urine, saliva or blood through radioimmuno assay are the best markers because only source could be tobacco smoke for non-smokers, and levels increase with increased exposure to tobacco smoke, it has

been demonstrated that increasing restrictions placed on where and when smoking in the house were significantly associated with lower urinary cotinine concentrations in children with asthma ***(Wong et al., 2002).***

Cotinine has become increasingly accepted as a short-term marker because of its relatively long half-life (approximately 20 hours, compared with approximately 2 hours for nicotine). It also is less susceptible to fluctuations during exposure to tobacco smoke and can be conveniently measured in blood, urine and saliva ***(Department of Health and Human Services. 1986 & National Research Council, Committee on Passive Smoking 1986).***

Cotinine measurements can provide an assessment of recent exposure to environmental tobacco smoke, but they do not indicate the duration of exposure nor do they indicate the intake of other components of tobacco smoke that may be more important ***(Hawamdeh et al., 2003)***.

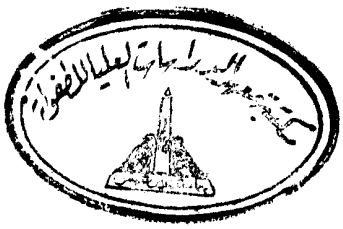
It has been estimated from cotinine measurements that the total nicotine dose received by children whose parents are smokers is equivalent to their actively smoking between 60 and 150 cigarettes per year ***(Working Party of the Royal College of Physicians 1992).***

Salivary cotinine concentrations measured in school-children have been found to correlate strongly with the smoking habits of their parents, particularly their mothers.

The measured cotinine levels correlate closely with atmospheric nicotine levels measured within the home and with the results of questionnaires about household smoking ***(Working Party of the Royal College of Physicians 1992)***, however, Strachan et al. ***(Strachan DP et al., 1990)*** also found significant levels of cotinine in children from non-smoking households.

This indicates that children are exposed to tobacco smoke from sources other than their parents and that simply inquiring about parental smoking will underestimate a child's exposure. So-called 'unexposed' persons have been found to have on average 8.5 ng of cotinine per mL of urine ***(Wald and Ritchie 1984)***.

Since the only source of cotinine or nicotine in body fluids is tobacco products, primarily through exposure to smoke, it follows that 'unexposed' persons are also exposed to environmental tobacco smoke ***(Hawamdeh et al., 2003)***.



Subject & Method

Subjects and Methods

This study was conducted (from January to June 2006) on eighty six children; their age ranged from 6-11 years old, from both sexes, they were divided into four groups;

Group I:

Included twenty two healthy children; neither exposed to environmental tobacco smoke nor to inhaled corticosteroids.this group was considered as control group.

Group II:

Included twenty four healthy children exposed to environmental tobacco smoke (parental smoking more than 10 cigarettes /day).

Group III:

Included twenty asthmatic children (with moderate persistent asthma) not exposed to tobacco smoke; attending Pediatrics Chest Clinic Ain-Shams University Hospital, they were on inhaled corticosteroids with a medium dose and duration not less than one year.

Group IV:

Included twenty asthmatic children (with moderate persistent asthma); attending Pediatrics Chest Clinic Ain-Shams University Hospital, on inhaled corticosteroids and exposed to tobacco smoke.

Inclusion criteria;

- For **group I**:

* Healthy children, proved by medical history and clinical examination.

* Not exposed to tobacco smoke.

- For **group II**:

* Healthy children, proved by medical history and clinical examination.

* Exposed to tobacco smoke at home for at least 3 years (one or both parents are smokers of more than 10 cigarettes / day).

- For **group III**:

*Asthmatic children with moderate persistent asthma with criteria according to GINA guidelines which are;

- Daily symptoms with daily use of B2-agonist.
- Attacks affect activity.
- Night time symptoms > 1 time/week.
- PEF > 60 & < 80.
- Variability of PEF >20 - 30 %.

* On Fluticasone 200-500 micgm or the equivalent dose of other inhaled corticosteroids and for duration not less than one year.

* Not exposed to tobacco smoke.

- For **group IV:**

* Asthmatic children with the same criteria of group III but exposed to tobacco smoke as group II.

Exclusion criteria;

- History of intake of systemic corticosteroids either for a period over 1 month or over the last 3 months before starting of the study.
- History of exposure to tobacco smoke for less than one year or less than 10 cigarettes /day.
- History of endocrinopathy, nephropathy or gastroenteropathy.
- Manifestations of malnutrition, anemia or chronic infestations.
- Short stature (below 10^{th} percentile) or obesity (body mass index (BMI) = weight/height^2 is above the 95^{th} percentile).
- Prolonged immobility period (more than two weeks).
- Over 11 years old to avoid the effect of pubertal hormonal changes.

Every patient was subjected to the following;

1) Full medical history; data were collected through a pre-designed questionnaire - in Arabic (Fig. 9)- which included:

- Personal history; Name, birth date, sex, address and phone number.
- History of asthma; symptoms (wheezes, cough, shortness of breath and chest tightness), hospital admission, emergency room, school absence, exercise induced asthma, previous and current treatment, daily symptoms and night symptoms. Questions were derived from The International Study of Asthma and Allergy in Childhood questionnaire ***(Galant SP et al., 2004).***

- History of corticosteroids therapy; type; whether inhaled or systemic, dose & duration.
- History of exposure to environmental tobacco smoke; paternal and maternal smoking, number of cigarettes/day, duration of exposure, possibility of exposure outside home, number of smoking household contacts and living area.
- Nutritional habits included number of meals and regular intake of sufficient amount of calcium in many kinds of food as milk, yougurt, orange, cheese, spinach and eggs.
- History of any medical problems as; thyroid dysfunction, anaemia, infestations, immobility, renal impairment and malnutrition.

Figure 9: Study Questionnaire (Arabic).

20

استمارة استبيان للاشتراك في تقييم كثافة العظام

الاسم:----------

تاريخ الميلاد: يوم ---------- شهر ---------- سنة ----------

العنوان:----------

رقم التليفون: ---------- المحمول: ----------

الطول: ---------- سم BMI : ----------

الوزن: ---------- كجم النوع: ---------- ذكر ام انثى ----------

1- فى خلال العامين الماضيين ، هل عانى طفلك من نوبات متكررة من اى الاعراض التالية ، (برجاء وضع دائرة حول كل الاجابات الملائمة):

- ازمة ربوية.
- كحة.
- صعوبة فى التنفس.
- ضيق بالصدر.
- التهاب بالشعب الهوائية.

2- فى خلال العامين الماضيين ، هل تم علاج طفلك فى غرفة الطوارئ او تم احتجازه بالمستشفى بسبب كحة او ضيق بالصدر او صعوبة فى التنفس او ازيز بالصدر (برجاء وضع دائرة حول اجابة واحدة):

- ابدا.
- مرة واحدة.
- مرتان.
- ثلاث مرات.
- اربع مرات او اكثر.

3- هل غاب طفلك عن المدرسة بسبب كحة او ضيق بالصدر او صعوبة فى التنفس او ازيز بالصدر (برجاء وضع دائرة حول اجابة واحدة):

- ابدا.
- اقل من ٥ ايام فى العام.
- ٥ – ١٠ ايام فى العام.
- اكثر من ١٠ ايام فى العام.

Figure 9 (cont.): Study Questionnaire (Arabic).

4- في اثناء اللعب او اداء الالعاب الرياضية هل عانى طفلك من نوبات كحة او ضيق بالصدر او صعوبة في التنفس او ازيز بالصدر (برجاء وضع دائرة حول اجابة واحدة):

- ابدا.
- نادرا.
- احيانا.
- غالبا.
- معظم الوقت.

5- في الاسابيع الاربعة الاخيرة ، هل استخدم طفلك العلاج(شراب- استنشاق – جهاز التنفس) لعلاج نوبة كحة او ضيق بالصدر او صعوبة في التنفس او ازيز بالصدر (برجاء وضع دائرة حول اجابة واحدة):

- ابدا.
- اقل من يومين في الاسبوع.
- يومين او اكثر في الاسبوع و لكن ليس كل يوم.
- كل يوم.
- اكثر من مرة في اليوم في معظم الايام.

6- في الاسابيع الاربعة الاخيرة ، هل عانى طفلك من نوبات كحة او ضيق بالصدر او صعوبة في التنفس او ازيز بالصدر في الصباح او خلال النهار (برجاء اختيار اجابة واحدة):

- ابدا.
- اقل من يومين في الاسبوع.
- يومين او اكثر في الاسبوع و لكن ليس كل يوم.
- كل يوم.
- اكثر من مرة خلال النهار في معظم الايام.

7- في الاسابيع الاربعة الاخيرة ، هل عانى طفلك من نوبات كحة او ضيق بالصدر او صعوبة في التنفس او ازيز بالصدر في المساء او اثناء النوم (برجاء اختيار اجابة واحدة):

- ابدا.
- اقل من مرة واحدة مساءا في الاسبوع.
- مرة واحدة مساءا في الاسبوع او اكثر ولكن ليس كل مساء.
- كل مساء.

Source: Stanley P., et al. Predictive Value of a Cross-Cultural asthma Case-Detection Tool in an Elementary School Population 2004.
Derived from, The International Study of Asthma and Allergy in Childhood questionnaire.

Figure 9 (cont.): Study Questionnaire (Arabic).

8- هل يستخدم الطفل بخاخات الكورتيزون: -------- نعم -------- لا
اذا كانت الاجابة بنعم فما نوعها: ----------
ما جرعتها: ----------
منذ متى: ----------

9- هل تم علاج الطفل بشراب او اقراص الكورتيزون من قبل: ------ نعم ------- لا
اذا كانت الاجابة بنعم فمتى: ----------
ما مدة العلاج: ----------

10- هل الأم مدخنة بالمنزل: ------ نعم -------- لا
اذا كانت الاجابة بنعم فمتى بدأت التدخين:---------- عام
ما عدد السجائر التى تدخنها بالمنزل (برجاء اختيار اجابة واحدة):
- اقل من ١٠ سجائر فى اليوم.
- من ١٠- ٢٠ سيجارة فى اليوم.
- اكثر من ٢٠ فى اليوم.

11- هل الأب مدخن بالمنزل: ------ نعم -------- لا
اذا كانت الاجابة بنعم فمتى بدأ التدخين:---------- عام
ما عدد السجائر التى يدخنها بالمنزل (برجاء اختيار اجابة واحدة):
- اقل من ١٠ سجائر فى اليوم.
- من ١٠- ٢٠ سيجارة فى اليوم.
- اكثر من ٢٠ فى اليوم.

12- هل يوجد مدخنين اخرين بالمنزل: ----- نعم ------- لا
اذا كانت الاجابة بنعم فما عددهم: ----------
ما عدد السجائر التى يدخنونها بالمنزل (برجاء اختيار اجابة واحدة):
- اقل من ١٠ سجائر فى اليوم.
- من ١٠- ٢٠ سيجارة فى اليوم.
- اكثر من ٢٠ فى اليوم.

13- ما عدد ساعات تعرض الطفل لدخان السجائر بالمنزل: --------

14- هل يوجد مكان اخر يمكن للطفل التعرض فيه لدخان السجائر: ----- نعم ------ لا
اذا كانت الاجابة بنعم فما هو: ----------
ما عدد ساعات تعرض الطفل لدخان السجائر: ----------

15- كم عدد المقيمين بالمنزل: ---------- شخص.

16- كم عدد حجرات المنزل: ---------- حجرة.

Figure 9 (cont.): Study Questionnaire (Arabic).

17- كم عدد وجبات الطفل فى اليوم: ---------- وجبة.

18- هل تحتوى وجبات الطفل بانتظام على المواد الغذائية الاتية (برجاء وضع دائرة حول كل الاجابات الملائمة):

- اللبن .... ماعدد الاكواب فى اليوم ---------- كوب.
- الزبادى .... ماعدد الاكواب فى اليوم ---------- كوب.
- الجبن بانواعه (جبن ابيض – شيدر – مطبوخ).
- السردين -- السلمون - التونة.
- البيض.
- عصير البرتقال.
- السبانخ.
- السودانى.

19- هل عانى الطفل من اى من الحالات المرضية التالية :

- خلل فى الغدد الصماء (الغدة الدرقية).
- امراض الكلى.
- ادوية (مضادات التشنج او مثبطات المناعة).
- كسور فى اى من اجزاء الجسم.
- عدم الحركة لفترة طويلة.
- انيميا او سوء تغذية.
- ديدان بالجهاز الهضمى.

2) Thorough clinical examination included;

A- General examination;

For signs of atopic diseases as allergic rhinitis, allergic conjunctivitis, allergic dermatitis and urticaria.

B- Local examination;

- Head and neck; pallor, cyanosis, eczema and evidence of allergic rhinitis.
- Chest; shape of chest, chest expantion, distress and retraction, breath sounds, wheezes and crepitiations.

C- Measurements;

- Height; it was measured by a calibrated wall-mounted stadiometer and was plotted against the stature for age reference charts for girls and boys (2-20 years) (Fig. 10&11) ***(CDC 2000).***
- Weight; it was measured using a calibrated electronic scale.
- BMI was calculated as weight (Kg) / height (m^2) and plotted against the body mass index -for- age reference charts for girls and boys (2-20 years) (Fig. 12 & 13) ***(CDC 2000).***

Figure 10:

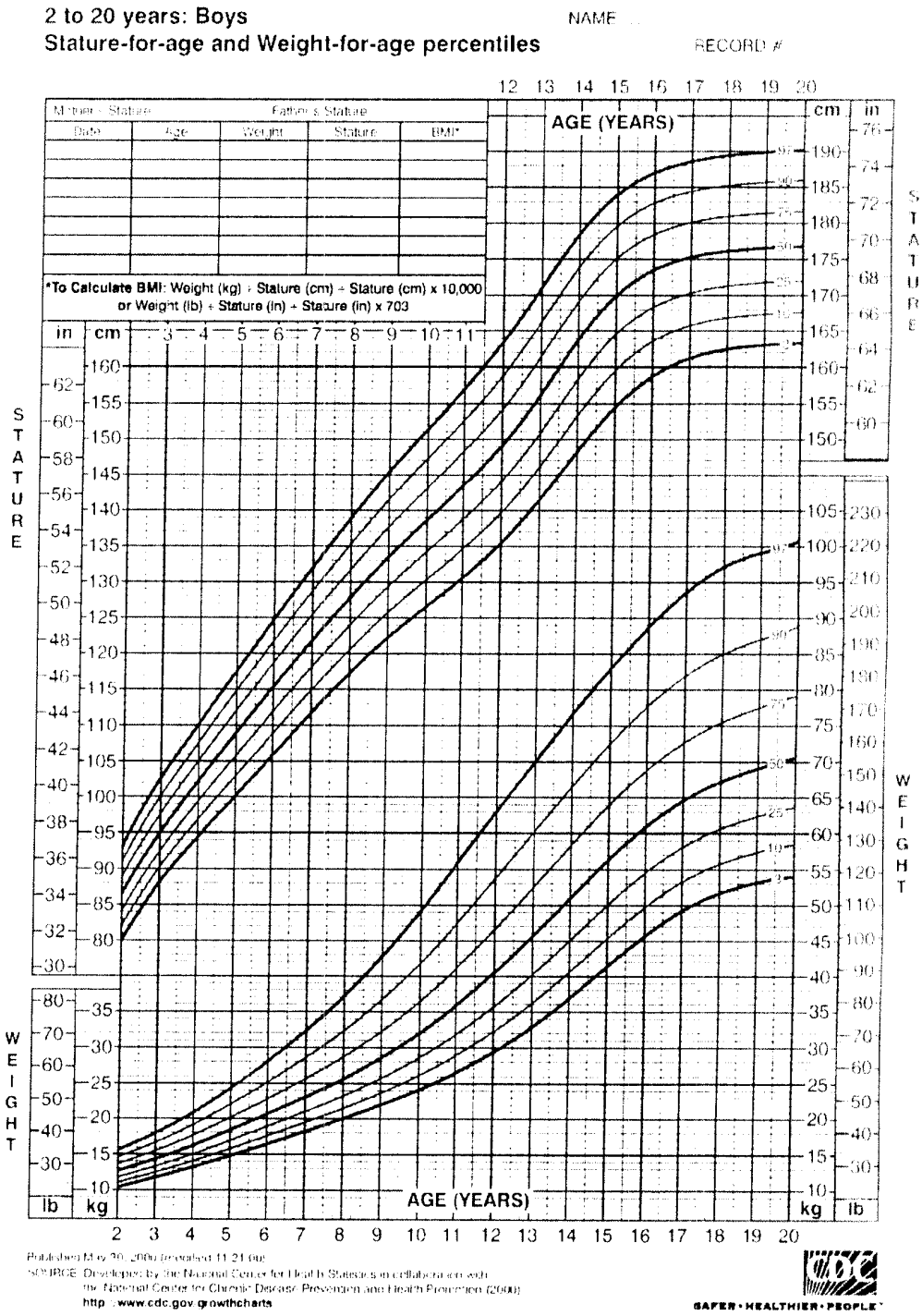


Figure 11:

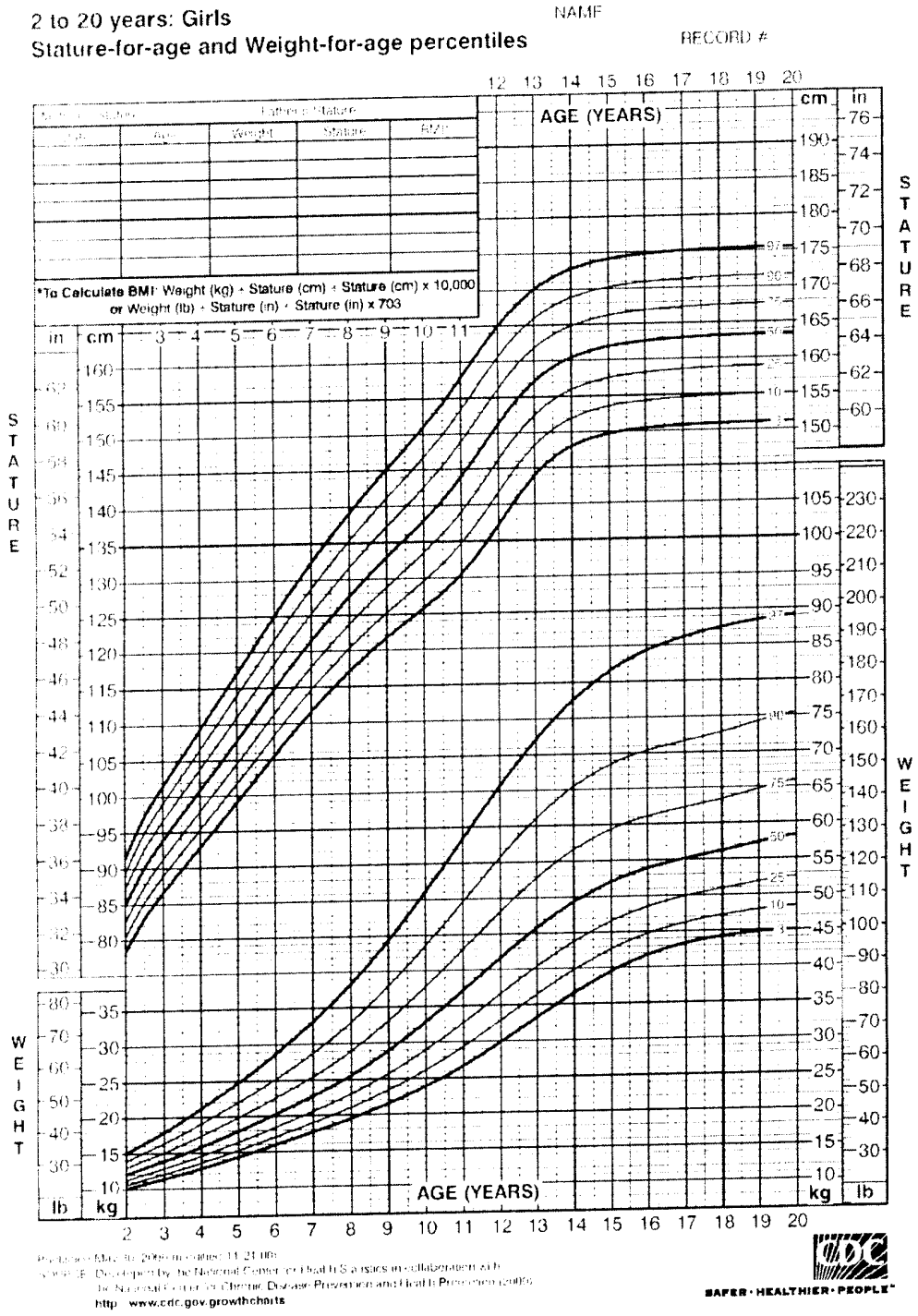


Figure 12:

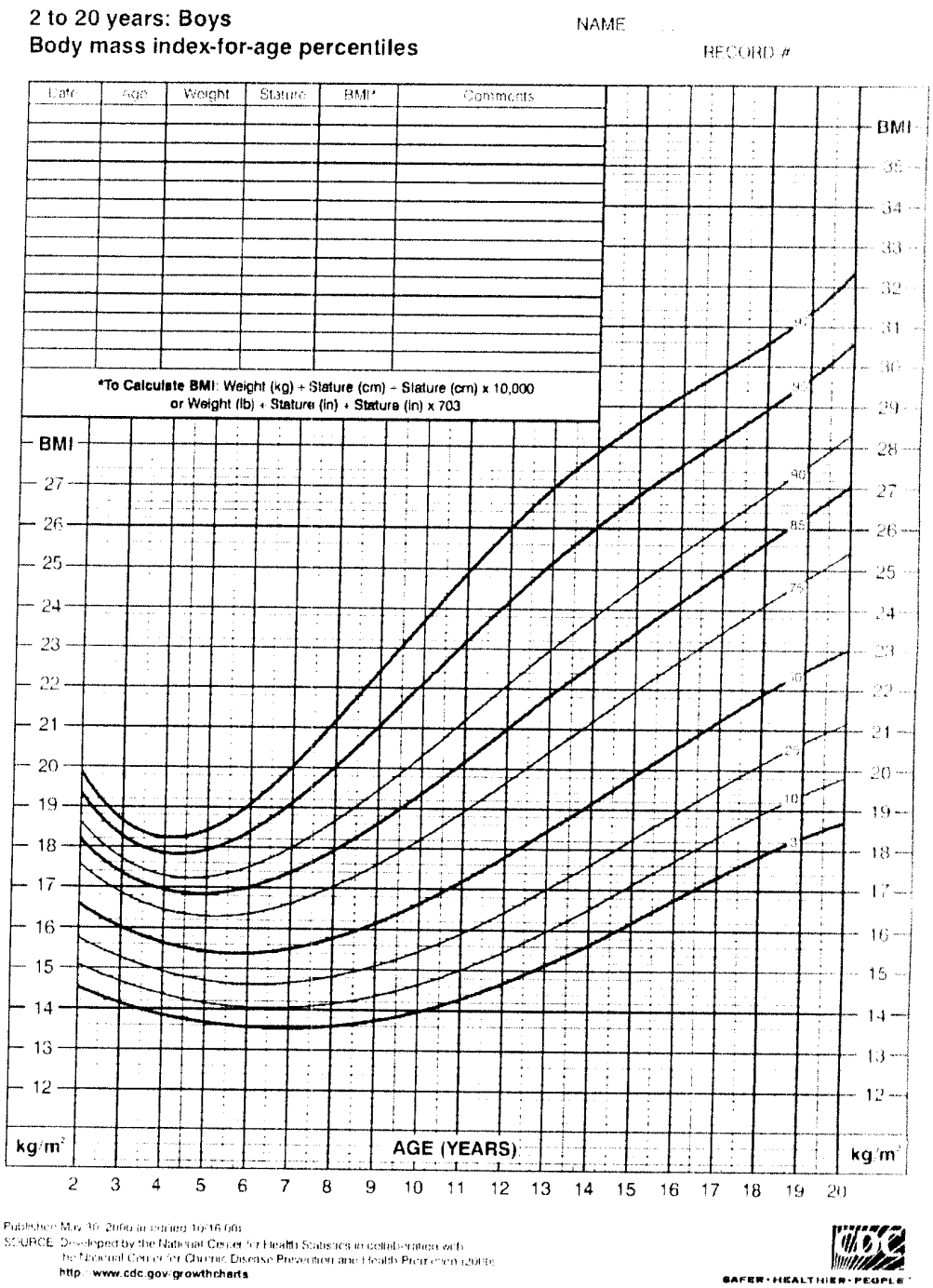
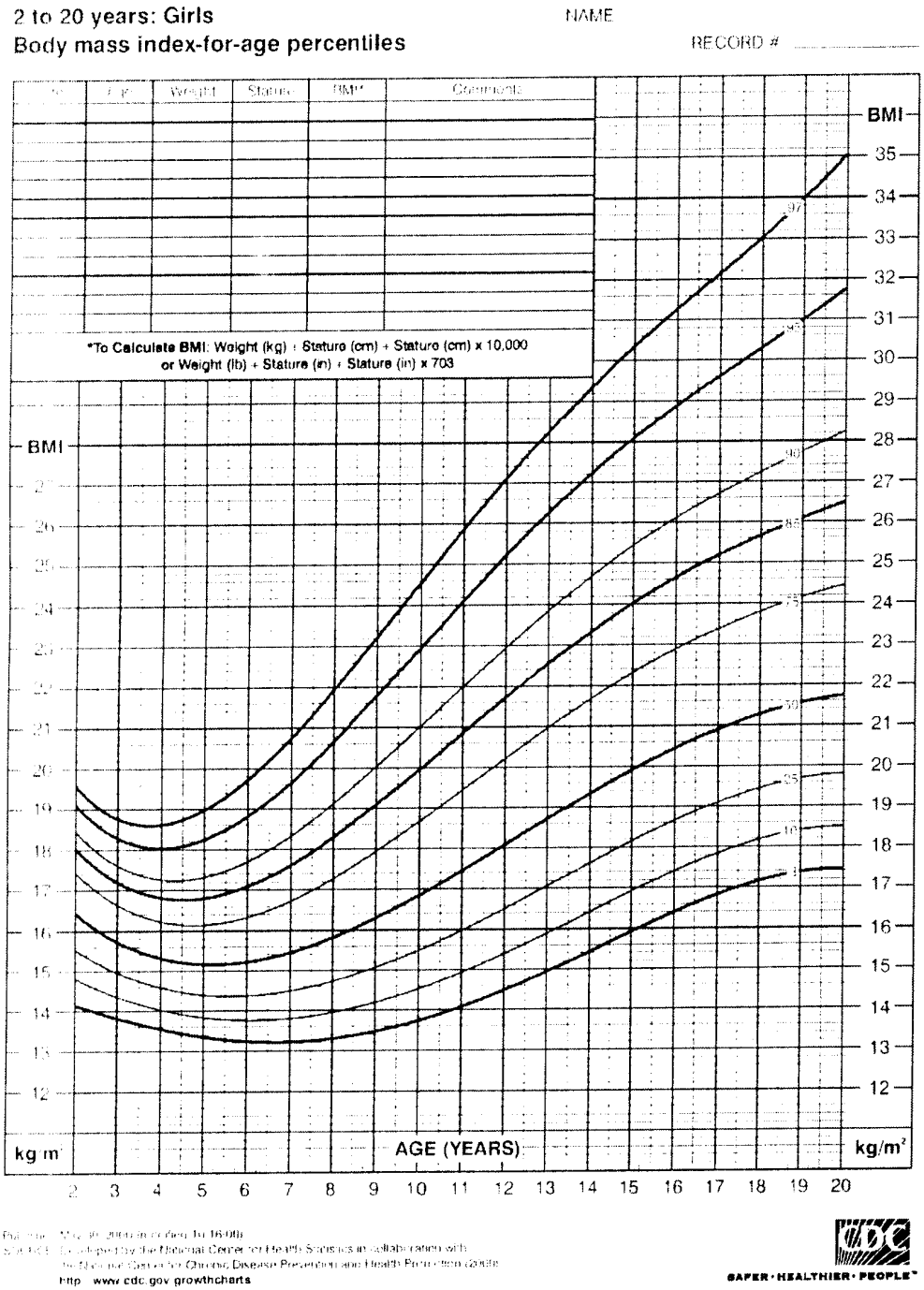


Figure 13:



3) Detection of level of exposure to environmental tobacco smoke by measuring urinary concentration of nicotine metabolite (cotinine) using The DRG Cotinine (Urine) ELISA -Enzyme Linked Immunosorbant Assay- (EIA-1377), which is a competitive micro-plate immunoassay for the qualitative and semi-quantitative determination of cotinine in urine. The test relies on the competition between free drug in the sample and drug bound to enzyme for antibody fixed on a polystyrene plate.

The following reagents were provided;

1- Anti-Cotinine Coated Plate - (1 plate)

Antibody immobilized on a plystyrene plate supplied in dry form.

2- Enzyme Conjugate - (15 ml)

Cotinine labeled with horseradish peroxidase and diluted in a protein matrix with stabilizers.

3- Substrate Reagent - (20 ml)

One bottle containing 3,3', 5,5' - tetramethylbenzidine.

4- Stopping Reagent - (20 ml)

One bottle containing 1 M sulfuric acid.

5- Wash Buffer Concentrate, 1 bottle (30 x) - (50 ml)

6- Negative Calibrator - Preserved human urine tested by GC/MS to be negative for cotinine.

7- Cotinine Negative Control - Preserved human urine containing 50 ng/ml (± 10%) cotinine and tested by GC/MS.

8- Cotinine Cutoff Calibrator - Preserved human urine containing 500 ng/ml (± 10%) cotinine and tested by GC/MS.

9- Cotinine Positive Control - Preserved human urine containing 5000 ng/ml (± 10%) cotinine and tested by GC/MS.

Urine samples were collected from the patients and stored frozen (-20°C), at the time of assay procedure, the following steps were followed to:

a- All samples and reagents came to room temperature (20-27°C) before use.

b- 10 microliters of sample, calibrator, or control were added to each test well.

c- Each well was labeled appropriately.

d- 100 microliters of Enzyme Conjugate was added to each test well.

e- Test wells were incubated for 30 minutes at room temperature (20-27°C).

f- The plate was washed using a suitable plate washer. As a general rule, each well should be washed 4 times with 350 microliters of diluted wash buffer.

g- 100 microliters of Substrate Reagent was added to each well and was incubated for 30 minutes at room temperature (20-27°C).

h- 100 microliters of Stopping Reagent was added to each well.

i- The absorbance was measured at a dual wavelength of 450 and 630 nm within 30 minutes of stopping the reaction.

The measured absorbance is inversely proportional to the amount of free drug in the sample;

- Positive Result; Any sample with an absorbance less than the Cutoff Calibrator (Calibrator 2) is considered as positive.

- Negative Result Any sample with an absorbance greater than the Cutoff Calibrator (Calibrator 2) is considered as negative.

A standard curve was prepared by plotting the absorbance values of the DRG Negative Calibrator and Calibrator 1-3 against the calibrator Cotinine concentrations. The absorbance values of positive samples were then compared to this standard curve.

4) The measurement of bone mineral density (BMD), expressed as gm/cm^2, and Z–score which is considered the reliable reference for assessing BMD in children as it is the number of standard deviations away from age-matched and ethnic-matched BMD; were obtained through a unit of DEXA (Dual-energy X-ray Absorptiometry, Prodigy, Lunar Radiation Corp.) using medium mode scan. The BMD was only studied at lumbar spine, since the evaluation of the femoral neck may be biased due to the presence of growth cartilage as well as to the technical difficulties related to the positioning and absence of the reference range in this age group.

1- A file was created to every patient on the soft ware of the machine including his/her personal data (name, date of birth, age, height, weight, sex, ethnic and study ID).

2- The patient was adjusted on the machine in the recommended position for measuring lumbar spines BMD; laying down on his/her back at right angle with raised thighs and the thighs at right angle with legs .

3- Laser beam was adjusted to start scanning two fingers below the umbilicus.

4- After the scanning finished, the recorded data was subjected to analysis.

5- A report was printed and given to the patient including; image of lumbar spines which is not for diagnosis, chart representing the measurement of the patient BMD plotted against reference ranges and ancillary data including bone mineral content (BMC), expressed as gm; area of the vertebral body of the L1-L4 segment, expressed as cm^2; bone mineral density (BMD), expressed as gm/cm^2; and Z-score (Fig. 14).

Data Management:

Data were collected, revised, verified then edited on P.C.

Data were then analyzed statistically using SPSS statistical package version (13).

The following tests were done:

1- Mean = $\bar{X}$

2- Standard deviation = SD

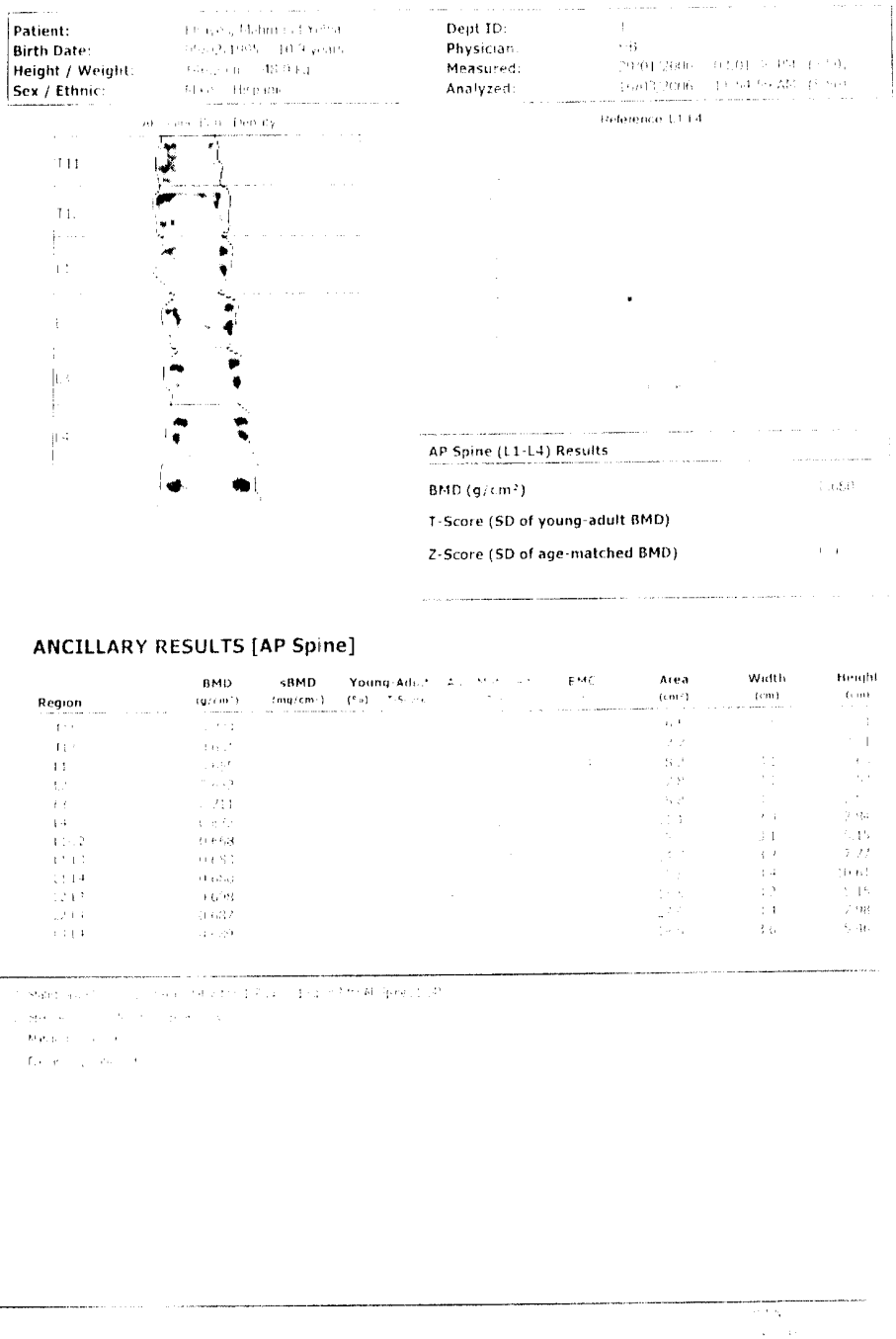
3- ANOVA = Analysis of variance

4- Chi square Test = X^2

5- T test for independent samples.

6- Pearson's Correlation Coefficient

Figure 14: AP Spine densitometry and ancillary results.



RESULTS

Eighty six children (aged 6-11 years) were enrolled in the study and were divided into 4 groups;

group I (Control): twenty two healthy children.

group II : twenty four healthy children but with the history of exposure to tobacco smoke.

group III: twenty children with moderate persistent asthma under inhaled corticosteroids therapy.

group IV : twenty children with moderate persistent asthma under inhaled corticosteroids therapy and with the history of exposure to tobacco smoke.

Level of exposure to environmental tobacco smoke was assessed by measuring cotinine (nicotine metabolite) in urine (ng/ml) using ELISA technique and both bone mineral density (gm/cm^2) and z-score of all the studied children were measured using DEXA unit.

Table 1:

Statistical comparison between the four studied groups as regards the age.

Age (Years)	Group I Controls (n = 22)	Group II ETS exposed (n = 24)	Group III Asthmatics (n = 20)	Group IV Asthmatics+ETS exposed (n = 20)
Mean ± SD	8.673 ±.355	8.433 ±.371	8.830 ±.383	8.532 ±.397
F	0.211			
P	> 0.05 (Non sig.)			

- n = Number
- SD = Standared Deviations

There was a non-significant statistical difference between the four groups (P > 0.05) as regards the age.

Figure 1:

Comparison between the four studied groups as regards the age.

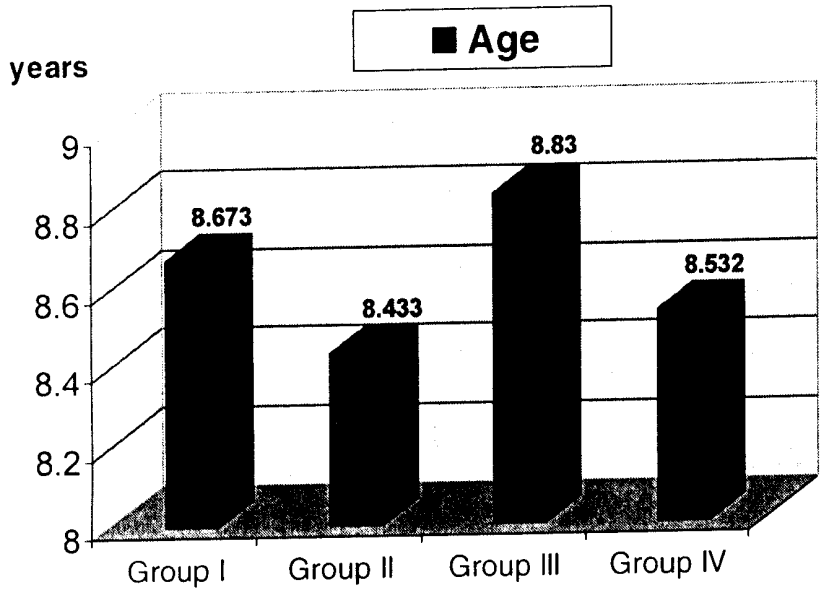


Table 2:

Statistical comparison between the four studied groups as regards the Sex.

	Group								Total
	Group I Controls		Group II ETS exposed		Group III Asthmatics		Group IV Asthmatics+ ETS exposed		
	n	%	n	%	n	%	n	%	
Sex M count	15	68.2 %	14	58.3 %	14	70 %	12	60 %	55
F count	7	31.8 %	10	41.7 %	6	30 %	8	40 %	31
Total count	22	100 %	24	100 %	20	100 %	20	100 %	86
Chi-Square X^2	0.952								
P	> 0.05 (Non sig.)								

- M = Male, F = Female

There was a non-significant statistical difference between the four groups (P > 0.05) as regards the sex.

Figure 2:

Comparison between the four studied groups as regards the sex.

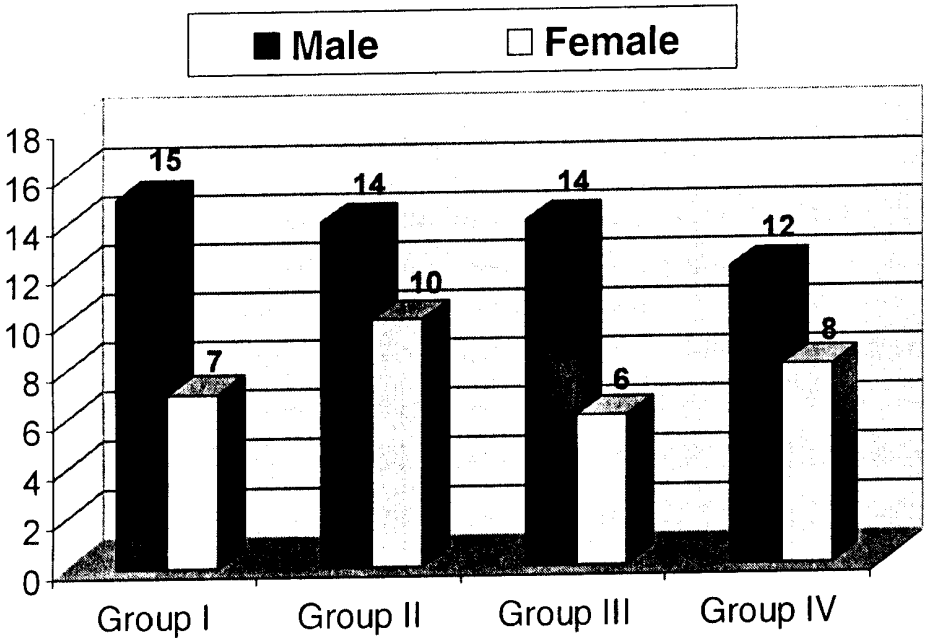


Table 3:

Statistical comparison between the four studied groups as regards the Body Mass Index (BMI).

Kg/m^2	Group I Controls (n = 22)	Group II ETS exposed (n = 24)	Group III Asthmatics (n = 20)	Group IV Asthmatics+ETS exposed (n = 20)
Mean ± SD	18.859 ± .571	17.544 ± .491	18.355 ± .715	17.705 ± .431
F	1.222			
P	> 0.05 (Non sig.)			

There was a non-significant statistical difference between the four groups ($P > 0.05$) as regards the Body mass index (BMI).

Figure 3:

Comparison between the four studied groups as regards the Body Mass Index (BMI) (Kg/m^2).

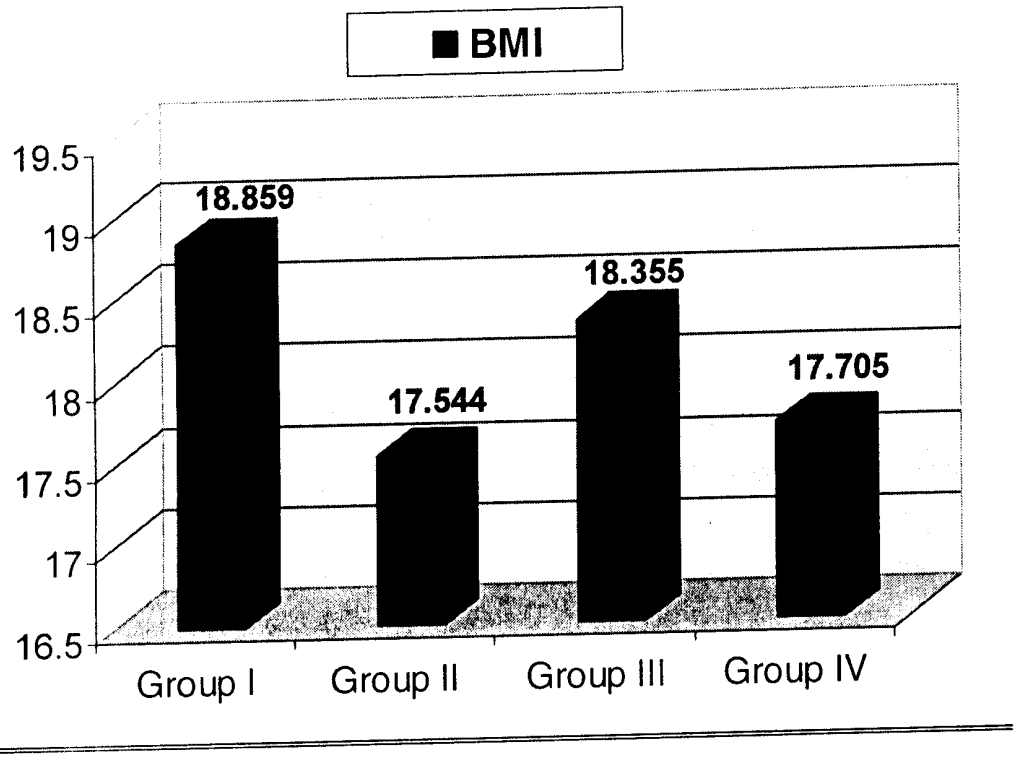


Table 4:

Statistical comparison between Group II and Group IV as regards the Cotinine Concentration (ng/ml)

Cotinine Concentration (ng/ml)	Group II (ETS exposed) n = 24	Group IV (Asthmatics+ETS exposed) n = 20
Mean ± SD	2259.333 ± 595.425	1834.182 ± 1306.971
t	0.747	
P	> 0.05 (Non sig.)	

There was a non-significant statistical difference between the group II and group IV ($P > 0.05$) as regards the cotinine concentration.

Table 5:

Statistical comparison between the four studied groups as regards Cotinine Concentration (ng/ml)

Cotinine Concentration (ng/ml)	Group I (Control) n = 22	Group II (ETS exposed) n = 24	Group III (Asthmatics) n = 20	Group IV (Asthmatics+ETS exposed) n = 20
Mean ± SD	53.932 ± 20.460	2259.333 ± 595.425	50.805 ± 19.326	1834.182 ± 1306.971
F	27.014			
P	< 0.001			

There was a highly significant statistical difference between the four studied groups (P< 0.001) as regards the cotinine concentration.

Figure 4:

Comparison between the four studied groups as regards Cotinine Concentration (ng/ml).

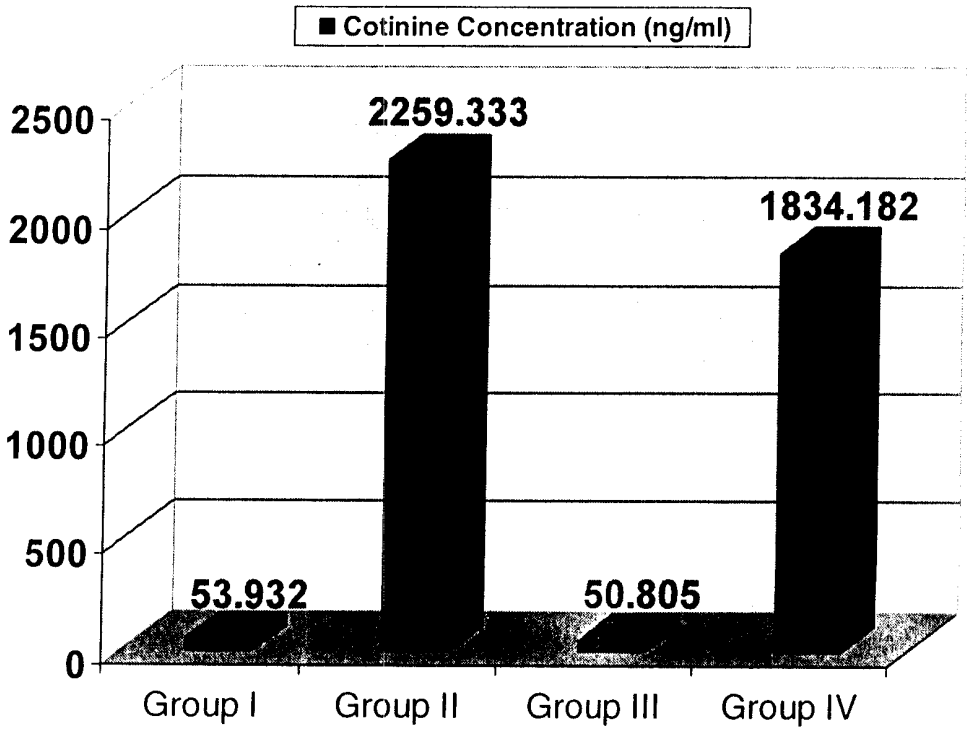


Table 6:

Statistical comparison between group III and group IV as regards Duration of ICS therapy.

Duration of ICS therapy (years)	Group III (Asthmatics) n = 20	Group IV Asthmatics+ETS exposed n = 20
Mean ± SD	2.225 ± .331	2.725 ± .396
t	0.968	
P	> 0.05 (Non sig.)	

- ICS = Inhaled corticosteroids.

There was a non-significant statistical difference between the group III and group IV ($P > 0.05$) as regards the duration of ICS therapy.

Table 7:

Statistical comparison between the four studied groups as regards the Bone Mineral Density (in terms of bone condition).

	Group								Total
	Group I Controls		**Group II** ETS exposed		**Group III** Asthmatics		**Group IV** Asthmatics+ETS exposed		
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	
Normal	17	34.0 %	11	22.0 %	12	24.0 %	10	20.0 %	50
Osteopenia	5	14.3 %	13	37.1 %	8	22.9 %	9	25.7 %	35
Osteoporosis							1	100 %	1
Total count	22	25.6 %	24	27.9 %	20	23.3 %	20	23.3 %	86
Chi-Square X^2	8.459								
P	> 0.05 (Non sig.)								

There was a non-significant statistical difference between the four studied groups ($P > 0.05$) as regards the Bone Mineral Density (in terms of bone condition).

Figure 5:

Comparison between the four studied groups as regards the Bone Mineral Density (in terms of bone condition).

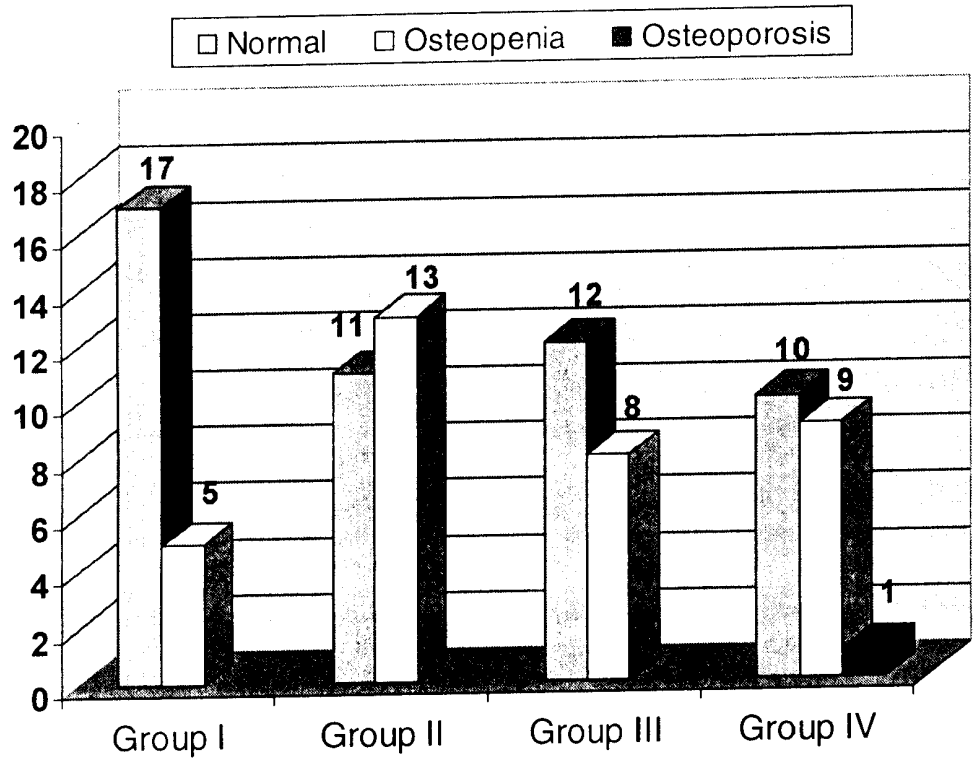


Table 8:

Statistical comparison between different sexes of group I as regards Bone Mineral Density (in terms of bone condition).

	SEX				Total
	FEMALE		MALE		
	n	%	n	%	
Normal	5	29.4 %	12	70.6 %	17
Osteopenia	2	40.0 %	3	60.0 %	5
Total count	7	31.8 %	15	68.2 %	22
Chi-Square X^2	0.200				
P	> 0.05 (Non sig.)				

There was a non-significant statistical difference between different sexes (Male & Female) in group I ($P > 0.05$) as regards the Bone Mineral Density (in terms of bone condition).

Figure 6:

Comparison between different sexes of group I as regards Bone Mineral Density (in terms of bone condition).

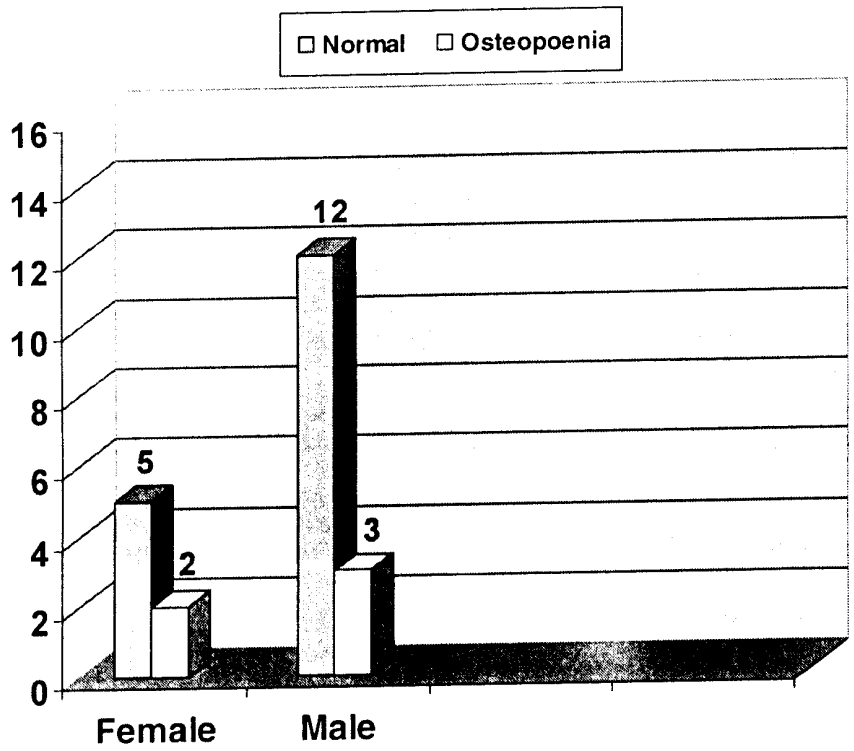


Table 9:

Statistical comparison between different sexes of group II as regards bone mineral density (in terms of bone condition).

	SEX				Total
	FEMALE		MALE		
	n	%	n	%	
Normal	3	27.3 %	8	72.7%	11
Osteopenia	7	53.8 %	6	46.2 %	13
Total count	10	41.7 %	14	58.3 %	24
Chi-Square X^2	1.731				
P	> 0.05 (Non sig.)				

There was a non-significant statistical difference between different sexes (Male & Female) in group II ($P > 0.05$) as regards the Bone Mineral Density (in terms of bone condition).

Figure 7:

Comparison between different sexes of group II as regards Bone Mineral Density (in terms of bone condition).

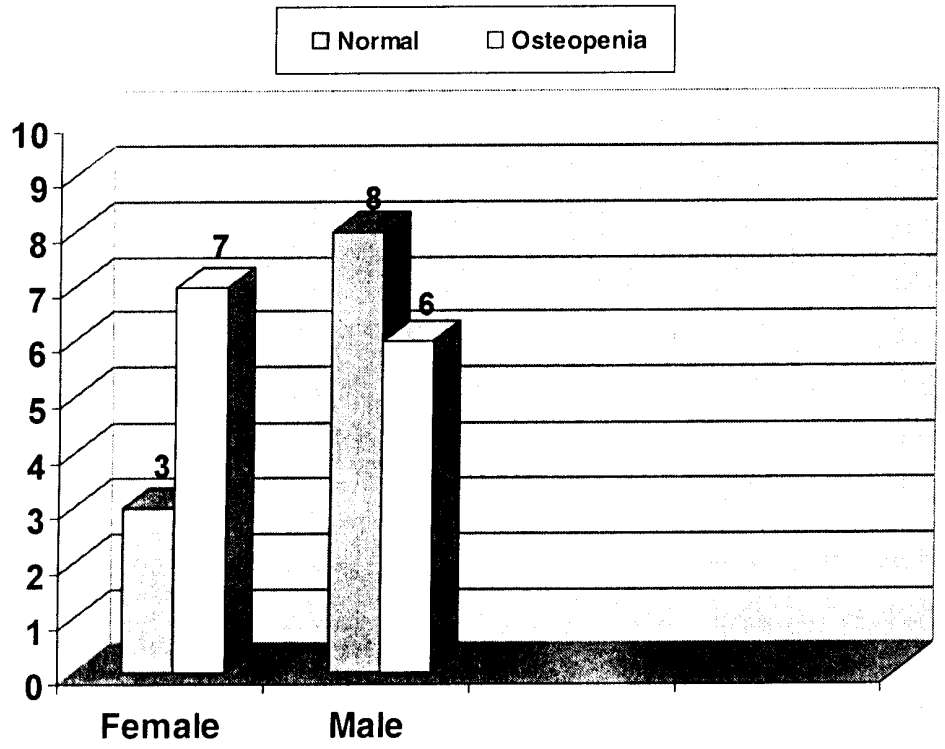


Table 10:

Statistical comparison between different sexes of group III as regards Bone Mineral Density (in terms of bone condition).

	SEX				Total
	FEMALE		MALE		
	n	%	n	%	
Normal	5	41.7%	7	58.3%	12
Osteopenia	1	12.5%	7	87.5%	8
Total count	6	30.0%	14	70.0%	20
Chi-Square X^2	1.944				
P	> 0.05 (Non sig.)				

There was a non-significant statistical difference between different sexes (Male & Female) in group III ($P > 0.05$) as regards the Bone Mineral Density (in terms of bone condition).

Figure 8:

Comparison between different sexes of group III as regards Bone Mineral Density (in terms of bone condition).

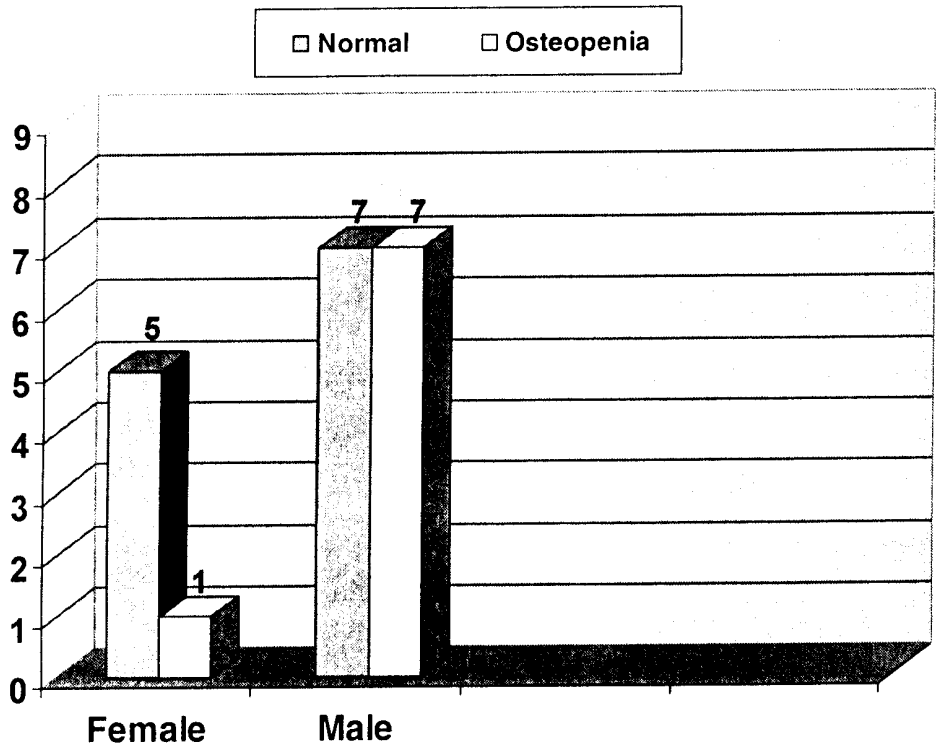


Table 11:

Statistical comparison between different sexes of group IV as regards Bone Mineral Density (in terms of bone condition).

	SEX				Total
	FEMALE		**MALE**		
	n	**%**	**n**	**%**	
Normal	4	40.0%	6	60.0%	10
Osteopenia	3	33.3%	6	66.7%	9
Osteoporosis	1	100.0%			1
Total count	8	40.0%	12	60.0%	20
Chi-Square X^2	1.66				
P	> 0.05 (NS)				

There was a non-significant statistical difference between different sexes (Male & Female) in group IV ($P > 0.05$) as regards the Bone Mineral Density (in terms of bone condition).

Figure 9:

Comparison between different sexes of group IV as regards Bone Mineral Density (in terms of bone condition).

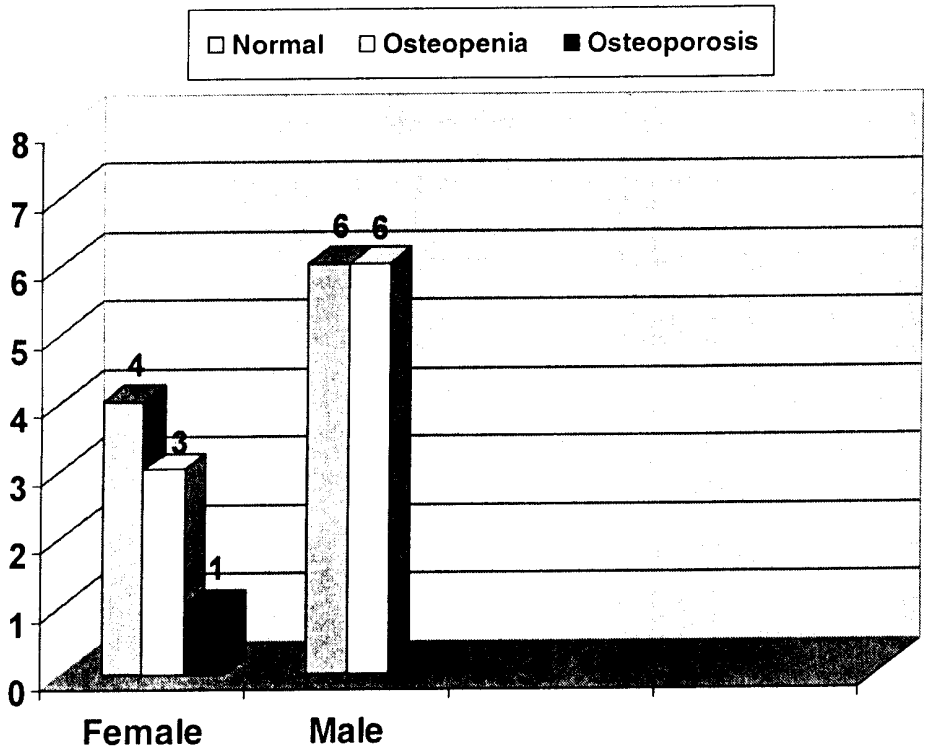


Table 12:

Statistical comparison between group I and group II as regards Bone mineral density (BMD) (g/cm^2).

BMD (g/cm^2)	**Group I** (Control) **n = 22**	**Group II** (ETS exposed) **n = 24**
Mean ± SD	.65695 ± 1.573	.61710 ± 1.875
t	1.134	
P	> 0.05 (Non sig.)	

There was a non-significant statistical difference between the group I and group II ($P > 0.05$) as regards Bone mineral density (BMD).

Table 13:

Statistical comparison between group I and group III as regards BMD (g/cm^2)

BMD (g/cm^2)	**Group I** (Control) **n = 22**	**Group III** (Asthmatics) **n = 20**
Mean ± SD	.65695 ± 1.573	.65525 ± 2.342
t	1.191	
P	> 0.05 (Non sig.)	

There was a non-significant statistical difference between the group I and group III ($P > 0.05$) as regards Bone mineral density (BMD).

Table 14:

Statistical comparison between group I and group IV as regards BMD (g/cm^2)

BMD (g/cm^2)	**Group I** (Control) **n = 22**	**Group IV** (Asthmatics+ETS exposed) **n = 20**
Mean ± SD	.65695 ± 1.573	.62275 ± 1.895
t	1.153	
P	> 0.05 (Non sig.)	

There was a non-significant statistical difference between the group I and group IV (P > 0.05) as regards Bone mineral density (BMD).

Table 15:

Statistical comparison between the four studied groups as regards BMD (g/cm^2)

BMD (g/cm^2)	Group I (Control) n = 22	Group II (ETS exposed) n = 24	Group III (Asthmatics) n = 20	Group IV (Asthmatics+ETS exposed) n = 20
Mean ± SD	.65695 ± 1.573	.61710 ± 1.875	.65525 ± 2.342	.62275 ± 1.895
F	1.021			
P	> 0.05 (Non sig.)			

There was a non-significant statistical difference between the four studied groups ($P > 0.05$) as regards Bone mineral density (BMD).

Table 16:

Statistical comparison between group I and group II as regards Z-Score

Z-score	Group I (Control) n = 22	Group II (ETS exposed) n = 24
Mean ± SD	-.662 ± .119	-.879 ± .143
t	1.313	
P	> 0.05 (Non sig.)	

There was a non-significant statistical difference between the group I and group II (P > 0.05) as regards Z-score.

Table 17:

Statistical comparison between group I and group III as regards Z-Score

Z-score	**Group I** (Control) **n = 22**	**Group III** (Asthmatics) **n = 20**
Mean ± SD	-.662 ± .119	-.645 ± .175
t	0.063	
P	> 0.05 (Non sig.)	

There was a non-significant statistical difference between the group I and group III ($P > 0.05$) as regards Z-score.

Table 18:

Statistical comparison between group I and group IV as regards Z-Score

Z-score	Group I (control) n = 22	Group IV (Asthmatics+ETS exposed) n = 20
Mean ± SD	-.662 ± .119	-.925 ± .182
t	1.563	
P	> 0.05 (Non sig.)	

There was a non-significant statistical difference between the group I and group IV (P > 0.05) as regards Z-score.

Table 19:

Statistical comparison between the four studied groups as regards Z-Score

Z-score	Group I (Control) n = 22	Group II (ETS exposed) n = 24	Group III (Asthmatics) n = 20	Group IV (Asthmatics+ETS exposed) n = 20
Mean ± SD	-.662 ± .119	-.879 ± .143	-.645 ± .175	-.925 ± .182
F	0.972			
P	> 0.05 (Non sig.)			

There was a non-significant statistical difference between the four studied groups (P > 0.05) as regards Z-score.

Figure 10:

Comparison between the four studied groups as regards BMD & Z-Score

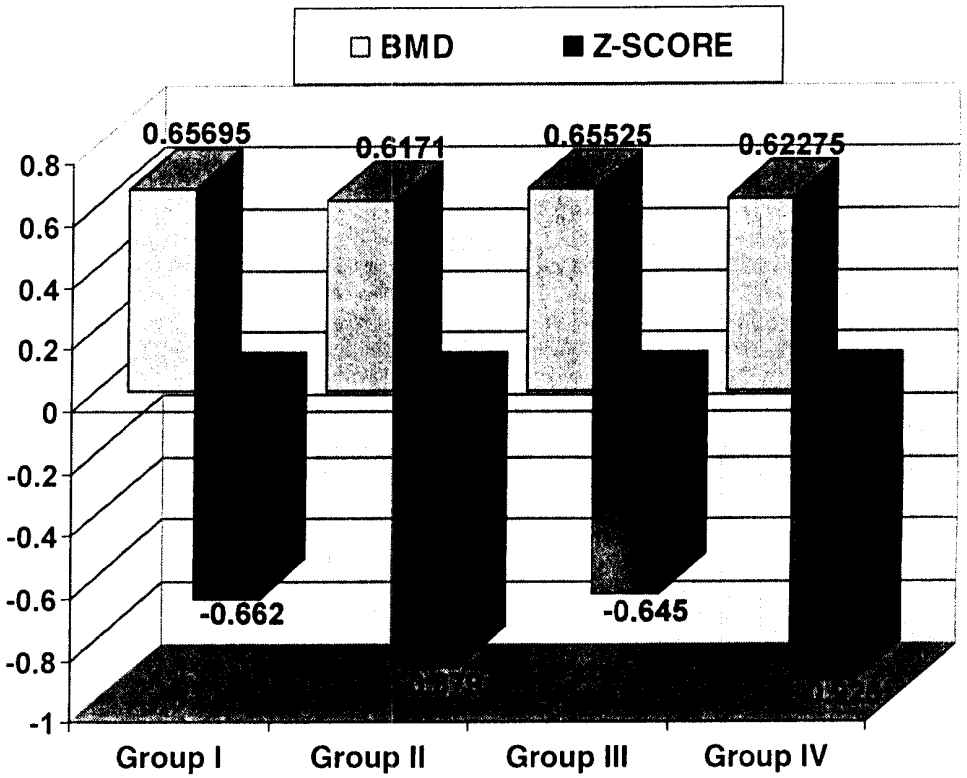


Table 20:

Correlation between BMD # AGE, BMI & Cotinine Concentration in group I

	AGE (Years)	BMI	Cotinine Concentration (ng/ml)
BMD (g/cm^2)			
r	0.630**	0.771**	0.047
P	< 0.05	< 0.001	> 0.05 (Non sig.)

There was a statistically significant +ve correlation ($P < 0.05$) between BMD and Age in group I.

There was a highly statistically significant +ve correlation ($P < 0.001$) between BMD and BMI in group I.

There was a statistically non-significant +ve correlation ($P > 0.05$) between BMD and Cotinine Concentration in group I.

Table 21:

Correlation between BMD # AGE, BMI & Cotinine Concentration in group II

BMD (gm/cm^2)	AGE years	BMI (Kg/m^2)	Cotinine Concentration (ng/ml)
r	0.672**	0.675**	-.781**
P	< 0.001	< 0.001	< 0.001

There was a highly statistically significant +ve correlation ($P < 0.001$) between BMD and Age in group II.

There was a highly statistically significant +ve correlation ($P < 0.001$) between BMD and BMI in group II.

There was a highly statistically significant -ve correlation ($P < 0.001$) between BMD and Cotinine Concentration in group II.

Table 22:

Correlation between Z- Score & Cotinine concentration in Group II

		Cotinine Concentration (ng/ml)
Z- Score		
	r	**-.722****
	P	**< 0.001**

There was a highly statistically significant -ve correlation ($P < 0.001$) between Z- Score and Cotinine Concentration in group II.

Table 23:

Correlation between BMD # AGE, BMI & Duration of ICS in Group III

BMD (gm/cm^2)	AGE (Years)	BMI (Kg/m^2)	Duration of ICS (Years)
r	0.696**	0.755**	-.411
P	< 0.001	< 0.001	> 0.05 (Non sig.)

There was a highly statistically significant +ve correlation ($P < 0.001$) between BMD and Age in group III.

There was a highly statistically significant +ve correlation ($P < 0.001$) between BMD and BMI in group III.

There was a statistically non-significant -ve correlation ($P > 0.05$) between BMD and duration of ICS in group III.

Table 24:

Correlation between Z- Score & duration of ICS in group III

		Duration of ICS (Years)
Z- Score	r	-.450*
	P	< 0.05

There was a statistically significant -ve correlation ($P < 0.05$) between Z-Score and duration of ICS in group III.

Table 25:

Correlation between BMD # AGE, BMI, Cotinine Concentration & Duration of ICS in group IV

BMD (gm/cm^2)	AGE (Years)	BMI (Kg/m^2)	Cotinine Conc. (ng/ml)	Duration of ICS (Years)
r	0.412	0.317	0.042	0.114
P	> 0.05 (Non sig.)	> 0.05 (Non sig.)	> 0.05 (Non sig.)	> 0.05 (Non sig.)

There was a statistically non- significant +ve correlation ($P > 0.05$) between BMD and Age in group IV.

There was a statistically non- significant +ve correlation ($P > 0.05$) between BMD and BMI in group IV.

There was a statistically non- significant +ve correlation ($P > 0.05$) between BMD and Cotinine Conc. in group IV.

There was a statistically non- significant +ve correlation ($P > 0.05$) between BMD and duration of ICS in group IV.

Table 26:

Correlation between Z- Score # Cotinine Concentration & Duration of ICS in group IV

		Cotinine Conc. (ng/ml)	Duration of ICS (Years)
Z- Score	r	0.034	-.103
	P	> 0.05 (Non sig.)	> 0.05 (Non sig.)

There was a statistically non- significant +ve correlation (P > 0.05) between Z- Score and Cotinine Conc. in group IV.

There was a statistically non- significant -ve correlation (P > 0.05) between Z- Score and duration of ICS in group IV.

DISCUSSION

In children the rate of bone modeling or turnover is much higher than in adults. Furthermore, in adults the skeletal mass is decreasing over time, while in children it is increasing over time until peak bone mass or density is reached in early adulthood. The increase in bone mass is not a constant process but varies with age and season of the year. The skeletal modelling or turnover rate and the retention of calcium are highest during spring and summer and during infancy and adolescence. Normally, most of the skeletal mass will be accumulated by late adolescence. Just as adult height in relation to predicted adult height is the most important outcome measure of growth in children, so fracture or maximal peak bone mass/density is probably the most clinically relevant outcome measure for assessing the influence of steroids on bones in children ***(Pedersen 2002).***

In addition to nutrition (including calcium intake), heredity (both parents), endocrine factors (sexual development), poor asthma control and physical activity appear to have profound effects on peak bone mass formation ***(Michaelsson et al., 1995, Valimaki et al., 1994, Slemenda et al., 1991& Glastre et al., 1990).*** Some chronic diseases have also been reported to be associated with reduced peak bone mass in children ***(König et al., 1993 & Albanese et al., 1990).*** The finding that delayed puberty itself is associated with a significantly lower peak bone mass/density ***(Finkelstein et al., 1996 & Finkelstein et al., 1992)***

which is particularly important in the clinical management of children with asthma as this condition is seen in many children with asthma and atopy, independent of treatment.

Obviously, these confounding factors must be considered when the effects of steroids on bone metabolism are assessed. Finally, children show a remarkable ability to repair steroid induced bone loss. Children <3 years with synacten-induced compression fractures of the spine had normal X-rays of the spine 5–10 years later ***(Hansen & Nøkkentved 1989).*** Such remodeling and repair are not seen in adults.

The present work was carried to assess the effect of inhaled corticosteroids and exposure to environmental tobacco smoke both individually and in combination on bone mineral density of children.

Eighty six children were enrolled in the study; fourty six non-asthmatic and fourty asthmatic children, the non-asthmatic children were subdivided into twenty two children with no history of exposure to environmental tobacco smoke (controls) and twenty four children with history of exposure to tobacco smoke.

The asthmatic children were attending the Out-Patient Chest Clinic, pediatric Hospital, Ain Shams University, for follow-up. They were subdivided into twenty children with no history of exposure to environmental tobacco smoke and twenty children with history of exposure to environmental tobacco smoke.

All children were examined in Women Health Center-Heliopolis, a private center with the most updated DEXA machine (Lunar-Prodigy); they were subjected to history taking by a pre-designed questionnaire, thorough clinical examination, anthropometric measurements, urine sample collection for measuring cotinine level and bone mineral density measurement.

This work showed that there was non significant statistical difference of BMD (bone mineral density which was expressed as gm/cm^2) between group I "controls" and group III "moderate persistent asthmatics who were all treated with inhaled corticosteroids -Fluticasone >200-500 µg or the equivalent dose of other ICS- for a mean duration of 2.225 years with unguarenteed correct technique of inhalation"; (t 1.191 and $P > 0.05$). The Z-score values -which are the number of standard deviations away from age-matched and ethnic-matched BMD-, between group I and group III, were statistically compared and revealed non significant difference as well (t 0.063 and $P > 0.05$). The previous results can be interpreted as there is **no effect of inhaled corticosteroids on BMD of asthmatic children compared to BMD of non-asthmatic children.**

The previous findings agree with Levina and colleagues ***(2004)*** who investigated the effect of high-dose inhaled corticosteroids on BMD in children (9-15 years) with severe asthma. Their study followed 20 patients receiving fluticasone propionate 500-1000 µg/day for a one-year period in order to assess

how inhaler technique affected BMD. At the start of the study, 95% of the children displayed osteopenia of the lumbar spine. After one year, children were grouped according to whether their inhalation technique was correct or incorrect. Those children with a correct inhalation technique had a normal BMD level according to age. However, patients with an incorrect inhalation technique showed increased osteopenia ***(Levina and Namazova 2004)***.

The researchers concluded that BMD in children with severe asthma does not appear to be adversely affected by high-dose inhaled corticosteroids when a correct inhalation technique is followed. Nonobservance of a correct technique, however, led to a decrease in BMD in such patients ***(Levina and Namazova 2004).*** These findings are important because of the difficulty in achieving good inhaler technique in children and the elderly, indicating that these groups of patients may be more at risk for inhaled corticosteroid-induced adverse events ***(Pedersen et al., 2004)***.

Several cross-sectional studies and prospective, longitudinal studies on much smaller groups of children treated for shorter periods of time with inhaled steroids have reported similar results ***(Boot et al., 1995, Hopp et al., 1995, Kinberg et al., 1994, König et al., 1993 & Kraemer et al., 1987).***

Medici et al (2000) compared the effects of fluticasone propionate 400 µg with beclomethasone dipropionate 800 µg and fluticasone propionate 750 µg

with beclomethasone dipropionate 1500 µg in 69 asthmatics over one-year. Little or no evidence of any important differences between these doses were seen on bone density or bone metabolism ***(Medici et al 2000)***.

A cross-sectional comparison of lumbar spine-bone mineral density was undertaken in 76 subjects after stratifying them according to dosage and administration route of corticosteroid. Children receiving more than 800 µg/day of inhaled corticosteroid plus intermittent oral corticosteroid had a significantly lower weight-adjusted lumbar spine-bone mineral density than children treated only with 400–800 µg/day of inhaled corticosteroid. Bone mass was similar in children not receiving any inhaled corticosteroid and those treated with 400–800 µg/day of inhaled corticosteroid ***(Harris et al., 2001)***.

From another point of view, ***Egan et al (1999)*** compared the effects of fluticasone propionate 1000 µg with beclomethasone dipropionate 2000 µg in patients with moderate to severe asthma on bone density over 2 years. Spinal vertebral bone density was normal at baseline and remained unaltered following two years of treatment with fluticasone propionate, but deteriorated by 3.3% in absolute terms following treatment with beclomethasone dipropionate (though remaining within the normal range) by quantitative CT, but remained unchanged by dual-energy x-ray absorptiometry. There was no change at any other limb or in any biochemical markers of bone metabolism. This study suggests that high doses

of long-term ICS may minimally decrease bone density, although there may be a differential effect between different corticosteroids ***(Egan et al 1999)***.

In this work, concerning group IV "moderate persistent asthmatics who were all treated with inhaled corticosteroids -Fluticasone >200-500 µg or the equivalent dose of other ICS for a mean duration of 2.725 years- and exposed to tobacco smoke", there were a non-significant statistical positive correlation between BMD and duration of inhaled corticosteroids (r .114 and P >0.05) and a non-significant statistical negative correlation between Z-score and duration of inhaled corticosteroids (r -.103 and P >0.05) but concerning group III "moderate persistent asthmatics" who were all treated with inhaled corticosteroids - Fluticasone >200-500 µg or the equivalent dose of other ICS for a mean duration of 2.225 years-, there were a statistically non-significant negative correlation between BMD and duration of inhaled corticosteroids (r -.411 and P >0.05) and a statistically significant negative correlation between Z-score and duration of inhaled corticosteroids (r -.450 and P <0.05) which can be interpreted as that **long term inhaled corticosteroids therapy seems to affect BMD of asthmatic children compared to age-matched and ethnic –matched non-asthmatic children.**

The previous findings agree with ***Galván Fernández et al (2007)*** who examined 151 children, aged between 1 and 17 years. There were 71 asthmatics treated with ICS for at least 6 months (group 1), 44 asthmatics treated occasionally

with ICS during exacerbations (group 2), and 36 healthy children (group 3). Bone mineral density (BMD) and markers of bone formation and resorption were measured. No differences in BMD were found between groups 1 and 2 but significant differences were found between groups 1 and 3 ($p = 0.003$). No differences were found in markers of bone formation and resorption among the groups. No association was found between BMD and the type, daily dose or accumulated dose of ICS. They concluded that ICS treatment in asthmatic children seems to affect BMD. Markers of bone formation and resorption are unaffected. Osteopenia in these children could also be related to other factors that increase bone resorption ***(Galván Fernández et al 2007)***.

Similarly, changes in the total bone mineral content in children treated with high doses of BDP (Beclomethasone dipropionate) or BUD (Budesonide) or FP (Fluticasone propionate) have been recently documented during 12 months of treatment ***(Visser et al., 2004 & Allen 2002).***

A review of ICS effects on bone showed no evidence of changes in bone markers or degradation in children treated with ICS in standard doses ***(Leone et al., 2003)***. Moreover, higher doses may cause significant changes in the bone turnover rate, but the occurrence of these changes during the treatment, which is usually short-term, deserves further studies ***(Irwin RS and Richardson 2006)***.

Similarly, ***Pedersen (2002)*** reported that low doses of inhaled corticosteroid are not associated with any changes in biochemical markers of bone

formation or degradation, whereas low doses of prednisolone (2.5–5 mg/day) and high doses of inhaled corticosteroids affect some of these markers adversely. Even if short-term studies show effects on markers of bone turnover, 4–5 years treatment with inhaled budesonide at an average daily dose of 400 µg is not associated with an increased risk of reduced bone mineral density, osteoporosis or fracture in children. Further controlled prospective studies are needed to assess the effect of long term treatment on peak bone density ***(Pedersen 2002).***

On the contrary, a long-term, prospective study found that total body BMD of children treated with 3–6 years of continuous inhaled budesonide at an average daily dose of around 500 µg was not different from the BMD of 112 children with asthma, who had never received inhaled or oral steroids ***(Agertoft and Pedersen 1998).***

Furthermore, bone density did not correlate with duration of budesonide treatment or current or accumulated dose of budesonide. These findings were corroborated in a prospective, randomized, double-blind study on 1000 children, which compared the changes in BMD over 4 years in three groups of children with mild asthma. No differences were found in increases in BMD between the group which received inhaled budesonide at a daily dose of around 400 µg, and the groups of children treated with nedocromil or placebo ***(The Childhood Asthma Management Program Research Group 2000).***

Similarly in a prospective, randomized and double-blind study, twenty-three steroid-naive children with moderately severe asthma, aged 5-10 yrs, were allocated either BDP (400 microg) or FP (200 microg). Bone mineral density (BMD) was measured at regular intervals over 20 months. None of the markers of bone turnover showed any change during the study period. BMD increased at normal rates with age ***(Rao et al., 1999).***

Asthmatic children treated with BUD (> 800 µg/day) for longer than 18 months ***(Boulet et al., 1994)***, or BUD (500 µg/day) for 4.5 years ***(Agertoft and Pedersen 1997 & Agertoft and Pedersen 1993)***, or BDP (300-800 µg/day) for 2 years ***(König et al., 1993)*** do not present reduction of BMD when compared to those treated with placebo or smaller doses of the respective ICS. In wheezing infants, the use of an intermittent treatment model with inhaled BUD (400 µg/day) did not determine significant changes in BMD ***(Bisgaard et al., 2006).*** In a recent review of the use of ICS in children with asthma, none of the four trials evaluating BMD presented a significant alteration ***(Pedersen 2006).***

Luengo et al (1997) measured BMD by dual energy x-ray absorptiometry in asthmatic patients treated with 300- 1000 µg inhaled beclomethasone or budesonide and compared with BMD of age-matched healthy subjects at 2 years. There were no significant difference in BMD loss between patients and healthy controls. They found no correlation either between inhaled steroid doses or duration of treatment and BMD values ***(Luengo et al 1997).***

Hopp et al (1995) reported that there is no evidence that the long-term treatment of children with ICS in low doses is associated with the reduction of BMD or with increased risk of osteoporosis or fracture ***(Hopp et al 1995).***

Our work showed non-significant statistical differences between the four studied groups as regards BMD (F 1.021 and P>0.05), non-significant statistical differences between group I "controls" and group II "non-asthmatics exposed to tobacco smoke with a mean duration of exposure of 8.433 years" (t 1.134 and P >0.05) and non-significant statistical differences between group I "controls" and group IV "asthmatics exposed to tobacco smoke with a mean duration of exposure of 8.532 years" (t 1.153 and P >0.05).

As regards Z-score, there were non-significant statistical differences between the four studied groups (F 0.972 and P>0.05), non-significant statistical differences between group I and group II (t 1.313 and P >0.05) and non-significant statistical differences between group I and group IV (t 1.563 and P >0.05).

On the other hand, concerning group IV "asthmatics exposed to environmental tobacco smoke with a mean cotinine concentration of 1834.182 ng/ml and a mean duration of exposure of 8.532 years ", there were non-significant statistical positive correlation between BMD and cotinine concentration (r .042 and P >0.05) and non-significant statistical negative correlation between Z-score and cotinine concentration (r -.034 and P >0.05) but

concerning group II "non-asthmatics exposed to environmental tobacco smoke with a mean cotinine concentration of 2259.333 ng/ml and a mean duration of exposure of 8.433 years", there were statistically highly significant negative correlation between BMD and cotinine concentration (r -.781 and P <0.001) and statistically highly significant negative correlation between Z-score and cotinine concentration (r -.722 and P <0.001) this can be interpreted as **exposure to tobacco smoke seems to have effect on BMD of exposed children.**

There are no available studies to assess the effect of exposure to tobacco smoke on BMD of children but there was one study assessing the effect of exposure to tobacco smoke which was undergone on 154 healthy premenopausal women (age range 40-45 years). BMD of the total hip, femoral neck, lumbar spine and total body was measured by dual-energy X-ray absorptiometry (DXA). Data were collected on exposure to household tobacco smoke from age 10 years to the present as well as on other lifestyle factors related to bone mass. It was found that 67.5% of the subjects had a history of household tobacco smoke exposure.

Subjects exposed to household tobacco smoke had a mean adjusted BMD that was significantly lower at the total hip (p = 0.021) and femoral neck (p = 0.018) compared with subjects who were not exposed. In addition, duration of household tobacco smoke exposure was negatively associated with BMD at the total hip (p = 0.010), femoral neck (p = 0.004), lumbar spine (p = 0.037) and total body (p = 0.031). Subjects exposed to household tobacco smoke for 15 years or

more had mean adjusted BMD that was 4% lower at the total body, and more than 8% lower at the total hip, femoral neck and lumbar spine, compared with subjects who were not exposed.

It concluded that household tobacco smoke exposure during adolescence and young adulthood was found to be negatively associated with BMD at the total hip and femoral neck, and duration of exposure was negatively associated with BMD at the total hip, femoral neck, lumbar spine and total body in premenopausal women ***(Blum et al., 2002).***

In another study on mice, there was measuring of various biomechanical properties of femurs and tibiae obtained from smoke-exposed and control mice to determine cigarette smoke influences on bone mass, structure, and strength. Growing female C57BL mice were exposed to sidestream cigarette smoke in a whole-body exposure chamber, set at 30 ± 2 mg smoke particulates/m^3 for 4 hours/day and 5 days/week for 12 consecutive weeks.

Elevated levels of urinary cotinine and pulmonary ethoxy-resorufin de-ethylase activity in smoke-exposed mice confirmed their effective exposure to cigarette smoke. There were no differences in body weight and physical size (length, medial-lateral and anterior-posterior widths, midshaft cortical area and thickness) of femurs and tibiae between smoke-exposed and control mice.

The femoral mid-shaft yield load, stiffness, yield stress, and modulus were, respectively 8%, 13%, 10%, and 14% lower ($P < 0.05$) in smoke-exposed

compared to control mice. The ultimate load and stress in mid-shaft femurs showed decreasing trends ($P < 0.1$) in smoke-exposed mice. In the femoral neck, the ultimate load and stiffness were 9% and 12% lower ($P < 0.05$) in smoke-exposed mice, respectively.

Further, micro-computed tomographic scanning of distal femoral bone volume/total volume (%) and trabecular thickness showed decreasing trends in smoke-exposed mice compared to the control group. It was concluded that exposure to tobacco smoke deteriorates some of the biomechanical properties of bone in growing female mice ***(Akhter et al., 2005).***

Concerning smoking and its effect on adult, Most epidemiologic studies have found that BMD in older male and postmenopausal female smokers is significantly lower than that in nonsmokers, even after the effects of age, body mass index, and other lifestyle factors have been accounted for ***(Sowers et al., 1997, Egger et al., 1996, Hollenbach et al., 1993, Cheng et al., 1993, Krall and Dawson-Hughes 1991, Stevenson et al., 1989, Seeman et al., 1983 & Hollo et al., 1979).***

The results obtained for BMD at various sites within the body differ across the various studies. In the study by Egger and associates ***(Egger et al., 1996)*** of English men and women aged 61 to 73 years, the lumbar spine BMD was 7% to 8% lower in both male and female smokers compared with the never-

smokers. At the femoral neck, the differences were smaller and not statistically significant.

However, male and female smokers in the Rancho Bernardo Study (aged 60-99 years) had significantly lower BMD at the hip (but not at the spine or radius) than the nonsmokers ***(Hollenbach et al., 1993).*** In the Dubbo Osteoporosis Epidemiology Study, tobacco use among men and women (average age, 70 years) was associated with a 5% to 8% reduction in BMD at both the hip and spine ***(Nguyen et al. 1994)***.

Results from both the Rancho Bernardo Study ***(Hollenbach et al., 1993)*** and the Dubbo study ***(Nguyen et al., 1994)*** indicated that cessation of smoking was associated with a BMD level between that of never-smokers and current smokers. These data suggest that cessation of smoking may be helpful in slowing or preventing bone loss even in the elderly.

Smoking seems to have little effect on the BMD of premenopausal women ***(Mazess and Barden 1991, McCullough et al., 1990, Jensen 1986, Rundgren and Mellstrom 1984 & Daniell 1976).*** A Spanish study of premenopausal women did report an 8% lowering of hip but not spine BMD associated with smoking more than 20 cigarettes per day ***(Ortego-Centeno et al., 1994).*** However, when the effects of age and body weight were considered, smoking was no longer a determinant of BMD.

An Australian study by Hopper and Seeman ***(Hopper and Seeman 1994)*** of female twins discordant for tobacco use has generated some of the most important information regarding the effects of cigarette use on BMD. Twin research allows precise matching within the twin pairs on age, sex, and genetic composition. With these major determinants of BMD removed from consideration, it becomes possible to examine more precisely the effects of lifestyle factors, such as smoking, on BMD.

Hopper and Seeman ***(Hopper and Seeman 1994)*** measured BMD at the lumbar spine, femoral neck, and femoral shaft in 41 pairs of female twins, aged 27 to 73 years, discordant by at least 5 pack-years of smoking. Among the 20 pairs who were discordant by 20 or more pack-years of smoking, the BMD in the heavier smoking twin was 9% lower at the lumbar spine, 6% at the femoral neck, and 6.5% at the femoral shaft. When all 41 twin pairs were considered, a discordance of 10 pack-years of smoking was associated with a 2% decrease in BMD at the lumbar spine and a 1% decrease at the femoral sites. After controlling for the effects of lifestyle factors (estrogen replacement therapy, oral contraceptive use, exercise, use of alcohol, weight, age at menopause, etc), these differences were not substantively changed.

Hopper and Seeman point out that the clinical significance of these relatively small decrements in BMD may be substantial. For instance, a woman who smokes 1 pack of cigarettes per day during her adult years will have a 5% to

8% lower BMD at the time of menopause than a woman who has never smoked. They estimate that a 10% decrement is equivalent to a 44% increased risk for hip fracture ***(Hopper and Seeman 1994)***.

In a study by Oncken et al ***(Oncken et al., 2006)***, postmenopausal women (n = 152) who smoked at least 10 cigarettes per day were randomly assigned to behavioral counseling and either nicotine or placebo patch for smoking cessation (3-month treatment with a 1-month taper) and followed for an additional year. The BMD at various sites (hip, spine, wrist, and total body), were measured at baseline and again 1 year after smoking cessation. Women who continuously abstained from smoking between the end of treatment and 1 year later (quitters) (n = 42) were compared with women who completed the study and continued to smoke (n = 77). Femoral trochanter BMD increased by 2.9% among quitters vs. 0.6% among continued smokers (p = 0.02). Total hip BMD increased by 1.52% among quitters vs. 0.43% among continued smokers (p = 0.03). It concluded that smoking cessation, relative to continued smoking, increases BMD at the femoral trochanter and total hip in postmenopausal women.

In a meta-analysis study of smoking and fracture risk in adult (men and women), risk ratios were significantly higher in men than in women for all fractures and for osteoporotic fractures, but not for hip fracture. Low BMD accounted for only 23% of the smoking-related risk of hip fracture. Adjustment for body mass index had a small downward effect on risk for all fracture outcomes.

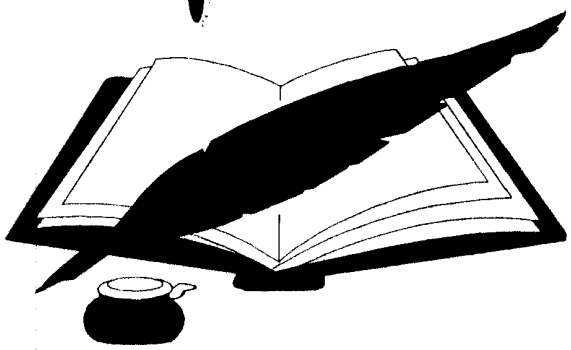
For osteoporotic fracture, the risk ratio increased with age, but decreased with age for hip fracture. A smoking history was associated with a significantly increased risk of fracture compared with individuals with no smoking history, but the risk ratios were lower than for current smoking ***(Kanis et al., 2005).***

A study was designed to estimate the modifiable distribution and determinants of bone mineral density (BMD) among Iranian women in Australia. Using T-scores from two bone sites (lumbar spines and femur neck), the prevalence of osteoporosis (T-scores $\leq$ -2.5) was 3.8% and 26.3% in pre-and post-menopausal women, respectively. Among current smokers, the prevalence was higher (31.3%) than that among ex-smokers (28.6%) and non-smokers (7.5%). It concluded that apart from advancing age and lower body mass index, cigarette smoking is an important modifiable determinant of bone mineral density in these Caucasians of non-European origin ***(Baheiraei et al., 2005)***.

A study aimed to investigate how a person's smoking habits in the premenopausal stage can affect the postmenopausal BMD values. Two hundred females in the postmenopause stage were evaluated. The average daily smoking habits in the premenopause stage and the demographic characteristics, age and duration of menopause of all the cases were identified and noted. The BMD values of the smokers' group were lower than non-smokers' group. As a result, advancing age, duration of menopause and smoking habits have been identified to be risk factors in relation to osteoporosis ***(Demirbag et al., 2006).***

Smoking has previously been associated with reduced areal bone mineral density (aBMD) in elderly subjects, but the association remains controversial in adolescents. The population-based Gothenburg Osteoporosis and Obesity Determinants (GOOD) study includes 1068 young men, age 18.9 +/- 0.6 yr (mean +/- SD). Bone parameters were compared between smokers and nonsmokers. Smokers had significantly lower aBMD (dual x-ray absorptiometry) of the total body (crude: -2.1%; adjusted for age, height, weight, calcium intake, and physical activity: -1.8%), lumbar spine (crude: -4.3%; adjusted: -3.3%), and trochanter (crude: -6.6%; adjusted: -5.0%) than nonsmokers. Adjustment for testosterone and/or 25-OH-vitamin D levels did not alter the associations between smoking and bone parameters. It was demonstrated that smoking was associated with lower aBMD and reduced cortical thickness in young men ***(Lorentzon et al., 2007)***.

Summary & Conclusion



SUMMARY AND CONCLUSION

The critical processes of skeletal growth and bone mineralization take place during childhood; reduced BMD may increase the risk for fractures in children and adolescents.

Asthma is a problem worldwide, it is the most common chronic illness of childhood, and inhaled glucocorticosteroids are the most effective controller therapy for asthma in children of all ages. Corticosteroid may affect bone metabolism through different mechanisms.

Environmental tobacco smoke (ETS) is the smoke present in the air that nonsmokers inhale; a large literature links both prenatal maternal smoking and children's ETS exposure to multiple serious health hazards.

The present work was done to detect the effect of Inhaled corticosteroids on BMD of asthmatic children, the effect of exposure to environmental tobacco smoke on BMD of healthy exposed children and the combined effect of both inhaled corticosteroids and exposure to environmental tobacco smoke on bone mineral density of asthmatic children.

Eighty six children; their ages ranged from 6-11 years from both sexes, were enrolled in the study; fourty six non-asthmatics and fourty moderate persistant asthmatics on inhaled corticosteroid therapy, the non-asthmatic children were subdivided into group I and group II.

Group I; twenty two children with no history of exposure to environmental tobacco smoke selected as controls; their mean age value was 8.673 ± .355 years, 68.2% were males and 31.8% were females, out of which 17 had normal BMD and 5 were osteopenic.

Group II; twenty four children with history of exposure to tobacco smoke; their mean age value was 8.433± .371 years, 58.3% were males and 41.7% were females, out of which 11 had normal BMD and 13 were osteopenic.

The asthmatic children were attending the Out-Patient Chest Clinic, pediatric Hospital, Ain Shams University, for follow-up. They were subdivided into group III and group IV.

Group III; twenty children with no history of exposure to environmental tobacco smoke; their mean age value was 8.830 ± .383 years, 70% were males and 30% were females, out of which 12 had normal BMD and 8 were osteopenic.

Group IV; twenty children with history of exposure to environmental tobacco smoke; their mean age value was 8.532 ± .397 years, 60% were males and 40% were females, out of which 10 had normal BMD, 9 were osteopenic and one was osteoporotic.

All children were subjected to history taking by a pre-designed questionnaire, thorough clinical examination, anthropometric measurements, urine sample collection for measuring cotinine level (ng/ml), bone mineral density (gm/cm^2) and z-score measurements.

There were non-significant differences between all groups as regards age, sex, BMD and z-score, yet there was a highly significant negative correlation between BMD and cotinine concentration and furthermore between z-score and cotinine concentration of children studied in group II which may indicate a probable effect of exposure to environmental tobacco smoke and BMD of children.

Another point of interest was the highly significant negative correlation between BMD and duration of inhaled corticosteroids therapy in children of group III which may indicate a probable effect of long term inhaled corticosteroids therapy on BMD of asthmatic children.

Although the results of group IV, as regards correlations between BMD and either inhaled corticosteroids or cotinine concentration, were somehow different from those derived from group II and group III, yet all are to be considered especially with the debate aroused between all the published papers concerning the effect of inhaled corticosteroids on BMD of children and the lack of available researches about the negative impact of exposure to environmental tobacco smoke on BMD of children.

Recommendations

RECOMMENDATIONS

1- Reference used for assessment of BMD was Spain AP Spine Reference Population for children, so it is highly recommended to start a plan in order to create our National Database which will help in proper evaluation and follow up.

2- Use of inhaled corticosteroids in asthma management carries a great range of safety, yet it is a must to have researches studying the possible side effects to ensure maximum safety of treatment.

3- Smoking is a catastrophic habit that may lead to life threatening events not only to smokers but also to exposed persons especially vulnerable groups as children, elderly and asthmatic populations so measures should be taken to ensure keeping clean air in closed places.

4- Further studies of exposure to environmental tobacco smoke health hazards are recommended, especially those correlated to pediatric age group and to bone condition in order to minimize the fracture risk in children.

5- Media should share in population-education of smoking hazards in order to minimize the negative impact on both adult and children.

6- Pediatricians should have the chance to educate parents the proper technique of ICS inhalation to ensure maximum effect with minimal side effects.

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Arabic Abstract

الملخص العربى

إن الزيادة فى متوسط عمر الانسان جعلت من مرض هشاشة العظام مشكلة صحية جديرة بالدراسة و تستمر عملية اكتساب كثافة العظام حتى نهاية مرحلة البلوغ مما أدى الى زيادة الاهتمام بدراسة محتوى العظام من المعادن اثناء فترتى الطفولة و المراهقة .

يعد الربو الشعبى من اكثر الأمراض المزمنة انتشارا فى الأطفال و قد اثبت العلاج باستنشاق الكورتيزون نتيجة فعالة فى علاج غالبية الحالات البسيطة و المتوسطة منه. و حيث ان هذه المجموعة الدوائيه ذات تأثيرات جانبية و منها تأثيرها على العظام فقد قامت العديد من الدراسات فى هذا الصدد.

حيث ان دخان التبغ يعد مشكلة بيئية خطيرة يدفع ثمنها المدخنين و المحيطين فقد اجريت العديد من الدراسات التى اثبتت احتوائه على مواد مسرطنة و تأثيره السلبى على الجهاز التنفسى و خاصة على الأطفال كما اثبتت تأثيره السلبى على كثافة العظام فى السيدات.

و لقد اجريت هذه الدراسة لبحث تأثير العلاج باستنشاق الكورتيزون على كثافة العظام فى الأطفال المصابين بالربو الشعبى و تأثير التعرض لدخان التبغ على كثافة العظام فى الأطفال و كذلك لبحث التأثير المزدوج للعلاج باستنشاق الكورتيزون و التعرض لدخان التبغ على كثافة العظام فى الأطفال المصابين بالربو الشعبى.

و قد اشتملت الدراسة على ستة و ثمانون طفلا تتراوح أعمارهم بين 6-11 عاما من الجنسين تم تقسيمهم الى اربع مجموعات كالتالى:

أ) اثنان وعشرون طفلا اصحاء و غير معرضين لدخان التبغ (مجموعة ضابطة).

ب) اربع و عشرون طفلا اصحاء و معرضين لدخان التبغ (أحد أو كلا الابوين من المدخنين).

ت) عشرون طفلا مصابا بالربو الشعبى(متوسط الحدة) – ممن يترددون على العيادة الخارجية للامراض الصدرية لمستشفى الأطفال بجامعة عين شمس للمتابعة – و يتم علاجهم باستنشاق مركبات الكورتيزون.

ث) عشرون طفلا مصابا بالربو الشعبى(متوسط الحدة) – ممن يترددون على العيادة الخارجية للامراض الصدرية لمستشفى الأطفال بجامعة عين شمس للمتابعة – و يتم علاجهم باستنشاق مركبات الكورتيزون و معرضين لدخان التبغ(أحد أو كلا الابوين من المدخنين).

خضع الأطفال الذين شملتهم الدراسة للآتى:

- أخذ التاريخ المرضى بالكامل عن طريق استمارة استبيان مسبقة الاعداد و تشمل أخذ تاريخ مرضى كامل للطفل و يشمل معلومات كاملة عن حالة الربو الشعبى (إن وجدت) و العلاج باستنشاق مركبات الكورتيزون (النوع،المدة، الجرعة) و كذلك عن التعرض لدخان التبغ (عدد المدخنين ، عدد السجائر / اليوم ، فترة التعرض) و العادات الغذائية.
- فحص اكلينيكى .
- قياس الطول و الوزن وحساب معامل كتلة الجسم.
- أخذ عينة بول لقياس مستوى الكوتينين و بالتالى قياس مستوى التعرض لدخان التبغ.
- قياس كثافة العظام لتقييم حالة العظام.

تم تحليل النتائج و ربطها احصائيا و قد أشارت نتائج البحث الى احتمال وجود علاقة بين زيادة مستوى التعرض لدخان التبغ و انخفاض كثافة العظام كما اشارت الى احتمال وجود علاقة بين زيادة مدة العلاج باستنشاق الكورتيزون و انخفاض كثافة العظام. و بالمقارنة بالأبحاث المماثلة فإن تأثير العلاج باستنشاق الكورتيزون ما يزال مجالا مستمرا للبحث بالرغم من تأكيد العديد من الدراسات على عدم وجود اى اثار جانبية له.

و فيما يختص بالعلاقة بين زيادة مستوى التعرض لدخان التبغ (التدخين السلبى) و انخفاض كثافة العظام فليست هناك اي ابحاث فى هذا الصدد فيما يشمل الأطفال وندرة فيما يشمل السيدات فى مرحلة ما قبل انقطاع الحيض على الرغم من وجود ابحاث تؤكد تأثير التدخين الإيجابى على كثافة العظام.

و نستخلص من هذه الدراسة أهمية تحديد الجرعة المناسبة من العلاج باستنشاق مركبات الكورتيزون حيث انه ذو كفاءة عالية و لكن يجب استخدام اقل جرعة ممكنة دائما لتجنب اى اثار جانبية.

كما يجب حماية الأطفال من التعرض لدخان التبغ (التدخين السلبى) لما فى ذلك من دور كبير فى الوقاية من العديد من المشاكل الصحية و من ثم نوصى بالقيام بالمزيد من الأبحاث و الدراسات الخاصة بالتعرض السلبى لدخان النيكوتين لقصور مثل هذه الأبحاث مقارنة بما يتعلق بالتدخين الإيجابى.

مستخلص

إن الزيادة فى متوسط عمر الإنسان جعلت من مرض هشاشة العظام مشكلة جديرة بالاهتمام وخاصة أثناء فترة الطفولة والمراهقة. يعد الربو الشعبى من أكثر الأمراض مزمنة انتشارا فى الأطفال كما يعد دخان التبغ مشكلة بيئية خطيرة يدفع ثمنها المدخنون والمحيطون بهم.

وقد أجريت الدراسة لبحث تأثير العلاج باستنشاق الكورتيزون والتعرض لدخان التبغ على كثافة العظام وشملت ٨٦ طفلا تم تقسيمهم إلى أربع مجموعات وتم تحليل النتائج وربطها إحصائيا حيث لم يوجد فارق بين المجموعات الأربع من حيث كثافة العظام ولكن بالتحليل وجد فى المجموعة المعرضة للدخان التبغ علاقة سلبية ذات دلالة بين مستوى التعرض وكثافة العظام وفى المجموعة المصابة بالربو ومن التعرض وجد علاقة سلبية ذات دلالة بين فترة العلاج وكثافة العظام.

الكلمات الكاشفة

- كثافة العظام
- الربو الشعبى
- دخان التبغ
- كوتينين
- مركبات الكورتيزون
- الاستنشاق

شكر

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وكذلك الهيئات الآتية :

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٢-

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الدرجة العلمية : دكتوراة

القسم التابع له : الدراسات الطبية

أسم المعهد : معهد الدراسات العليا للطفولة

الجامعة : عين شمس

سنة التخرج : ٢٠٠٨

سنة المنح : ٢٠٠٨

رسالة : دكتوراة

اسم الطالبة : هبه محمود بركات جاد

عنوان الرسالة : (تاثير الكورتيزون بالاستنشاق والتعرض لدخان التبغ على كثافة العظام فى الاطفال)

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٢٦ / ١٢ / ٢٠٠٧

موافقة مجلس المعهد موافقة مجلس الجامعة

٢٠٠ / / ٢٠٠ ٨/ ١ /٢٢

معهد الدراسات العليا للطفولة
قسم الدراسات الطبية

تأثير الكورتيزون بالاستنشاق و التعرض لدخان التبغ على كثافة العظام فى الأطفال

رسالة مقدمة توطئة للحصول على درجة دكتوراه دراسات الطفولة
قسم الدراسات الطبية - معهد الدراسات العليا للطفولة

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