AGENCY RESEARCH CONTRACT NUMBER: 8195/RB

TITLE OF PROJECT

" DETERMINATION OF PEAK BONE MASS DENSITY AND COMPOSITION IN LOW-INCOME URBAN RESIDENTS OF METRO MANILA USING ISOTOPE TECHNIQUES "

Part of Coordinated Programme:

COMPARATIVE INTERNATIONAL STUDIES OF OSTEOPOROSIS USING ISOTOPE TECHNIQUES

CONTRACTING INSTITUTE

PHILIPPINE SOCIETY OF ENDOCRINOLOGY AND METABOLISM
ENDOCRINE MEDICAL RESEARCH LABORATORY
UP-PGH MEDICAL CENTER
TAFT AVE., MANILA 1000
PHILIPPINES

CHIEF SCIENTIFIC INVESTIGATOR

MARY-ANNE V. LIM-ABRAHAN, M.D.

STARTING DATE OF CURRENT CONTRACT

November 1, 1994

TITLE OF PROJECT

" DETERMINATION OF PEAK BONE MASS DENSITY AND COMPOSITION IN LOW-INCOME URBAN RESIDENTS OF METRO MANILA USING ISOTOPE TECHNIQUES "

AUTHORS

Mary-Anne V. Lim-Abrahan, M. D.
Chief Scientific Investigator
Section Chief
Section of Endocrinology
Department of Medicine
UP - PGH Medical Center
Taft Ave., Manila 1000
Philippines
Tel. No. 521-84-50 local 3230
Fax: (632)-58-24-22

Ma. Luz Vicenta V. Guanzon, M. D.
Endocrine Section
UP - PGH Medical Center
Taft Ave., Manila 1000
Philippines

Angel M. De Guzman, M. D.
Chief
Nuclear Medicine and Radioisotope Laboratory
St. Luke's Medical Center
E. Rodriguez Ave., Quezon City
Philippines

Copernico M. Villaruel, M. D.
Department of Orthopedics
UP - PGH Medical Center
Taft Ave., Manila 1000
Philippines

Ma. Flora Santos, M. Sc.
Head, Analytical Measurements
Philippine Nuclear Research Institute
Marcos Ave., Quezon City
Philippines

ABSTRACT

Filipinos are predisposed to osteoporosis because of inadequate calcium in their diet early on in life, confounded by malnutrition, susceptibility to infectious diseases and their generally small body frame. And yet the problem of osteoporosis

has not been properly addressed. The incidence of osteoporosis is not known since oftentimes it is established only once complications have set in. It is believed that osteoporosis poses a public health concern but its extent is not realized at present because of lack of local epidemiological data.

This study aims to determine the bone mass density as a function of age among 210 screened and healthy volunteers coming from urban poor communities of Metro Manila over a 3-year period. A LUNAR DPX-L bone densitometry for dual X-ray photon absorptiometry will be used, with measurements taken on the spine and femur. It also aims to correlate factors such as nutritional intake, physical activity, lifestyle, sex and body mass index with that of bone mass density. Blood and urine samples will be obtained for biochemistry and hormonal radioimmunoassay examination. Statistical analysis will be done to compare differences within the group and to determine rate of bone loss as a function of age and sex. Plans for future research include the determination of trace element content in cortical bone and tooth samples from healthy living subjects.

1. SCIENTIFIC BACKGROUND AND SCOPE OF THE SUBJECT

1.A. OVERVIEW OF THE NATIONAL HEALTH SITUATION

Only 3.8% of our national budget is allocated for health [1]. In a country where 55 persons still die of tuberculosis and 1277 children still die of pneumonia everyday [2], it is understandable why our national health programs are geared towards battling infectious diseases. Osteoporosis as a public health concern is therefore not a priority of the Department of Health.

Aside from infectious diseases, renal and endocrine diseases which affect bone metabolism also burden the Filipinos. For the year 1988, 8.4/100,000 deaths were due to renal diseases, while 6.0/100,000 were due to thyrotoxicosis, hypothyroidism, other endocrine and metabolic disorders [3]. Goiter due to iodine deficiency is even endemic in our country [4]. In the Philippine General Hospital Outpatient Department alone, the prevalence of endocrine disorders is approximately 10,000/543,300 admissions per year, and that of renal diseases is approximately 5,000/543,300 admissions per year [5]. Furthermore, it it estimated that less than 10% Filipino women at their post-menopausal age receive hormonal replacement therapy [6]. These figures are not surprising since 76% of the rural population and 50% of the urban population do not have access to medications [7].

More than 50% of our children, considered the most vulnerable population, are malnourished [8]. The average Filipino worker with a GNP per capita of $727 [9] spends almost 50% of his daily income on food [10], yet this is clearly not adequate since

his daily caloric intake, on the average, amounts to less than 1800 kcal/day or only 87% of the recommended daily caloric intake. Aside from protein-energy inadequacy, the Filipino diet lacks other nutrients such as iron, thiamine, niacin, riboflavin, fats, and ascorbic acid. A Filipino consumes only 420-450 mg/day of calcium, way below the recommended allowance of 1000 mg/day [11].

The inadequacy of calcium and vitamin D in the diet is however alleviated by the fact that the Philippines enjoys adequate sunshine throughout the year and our vast coastal lines provide rich sources of calcium from seafoods and fishbone. The latter however is not popularly enjoyed by those living in mountainous areas. Dairy products are not readily available to the majority of the population, especially those in the rural areas because of lack of storage facilities, and its prohibitive cost to the average Filipino. Children do not usually receive enough milk after they have been weaned from breastfeeding at the age of 2 years, and milk-drinking is not a habit inculcated among adults. Lactose intolerance may also be common among Filipinos, although there are no exact figures to support this.

1.B. RATIONALE

In the Philippines, osteoporosis is often overlooked and neglected even by physicians. Moreoften, the diagnosis is established only when patients consult late, that is, when complications such as fractures, have already set in.

Osteoporosis exacts a great toll of suffering and health care costs. In the United States, at least 1.3 million cases of vertebral fracture per year are attributed to osteoporosis, with the cost of care on femoral fracture alone amounting to $ 5 billion [12]. There are no local figures currently available on the incidence of osteoporosis. In the Philippine General Hospital, a tertiary care government referral center with a bed capacity of 1,487, the incidence of osteoporosis as primary diagnosis among patients consulting at the Outpatient Department for the year 1993 is only 7/543,700 admissions, while that of hip fractures is 40/30,870 inpatient admissions/year [5, 13]. But whether these data reflect the trend on a nationwide scale has not been determined. It is estimated that each patient confined in a government hospital spends P 15,000.00 ($ 625) on surgical needs and antibiotics alone, while the government spends for the same amount as counterpart. This excludes the cost of lost opportunities and productivity on his part.

Foreign literatures have shown [14,15,16] that low bone mass density measurements is predictive of fracture. Melton et. al. [17] has introduced a concept for fracture risk assessment which could be useful in osteoporosis prophylaxis and patient manage-

ment. Thus, osteoporosis is preventable if reliable age-specific bone loss rates estimated from BMD is available. The variability in genetic and environmental factors among different races necessitates that a BMD curve as a function of age and sex must be derived from among Filipinos.

This study aims to determine the peak bone mass density among healthy Filipinos of varying ages. This study will hopefully complement the previous study done by Redoblado, De Guzman, et. al. [18]. These studies will hopefully serve as initiative towards coordinated efforts to address the problem of osteoporosis in our country.

1.C. RELEVANT WORK ON CRP

The availability of dual energy X-ray photon absorptiometry (DEXA) in Manila since 1993 has brought the attention of local researchers to focus on osteoporosis in the Philippine setting, albeit still at the inception stage. In the Philippine General Hospital, the Section of Reproductive Endocrinology has an ongoing research on the administration of gonadotropin releasing hormone on pre-menopausal women with endometriosis and endometriomas and its effect on bone mass density [19]. A study on the effect of hormonal replacement therapy on bone mass density among post-menopausal women [20] likewise shows very encouraging results, although it is still in progress. A multicenter study on the effect of calcitonin on post-menopausal osteoporotic women is still ongoing [21]. The BMD among 216 women who were referred for DEXA was reviewed at St. Luke's Hospital between the period February 1993 to August 1994. The subjects were considered high-risk i.e. those receiving steroids, long-term suppression therapy of levo-thyroxine, with history of fractures, post-menopausal women. The results showed a high prevalence of fractures and osteoporosis which reflect the population bias in this study [18].

1.D. COLLABORATIVE EFFORTS

At present, the Philippine Society of Endocrinology and Metabolism is addressing the problem of osteoporosis in the country. Efforts are underway to organize an Osteoporosis Society which will bring together different fields of specialty in Medicine in the Philippines to support campaigns for the prevention and alleviation of osteoporosis, and to encourage researches on this subject matter. The key figures from the PSEM, the Section of Endocrinology, Section of Reproductive Endocrinology, Department of Orthopedics, Nuclear Medicine in the Philippine General Hospital are in close coordination with those from other institutions such as the National Orthopedic Hospital, St. Luke's Medical Center, and the Philippine Nuclear Research Institute on this project.

2. METHODS

2.A. STUDY DESIGN

This is a prospective study scheduled to commence on November 1, 1994 and is projected to be finished within a 3-year period. The target for Year 1 is 90 subjects, Year 2 is 60 subjects, and Year 3 is 60 subjects.

2.B. SELECTION OF SUBJECTS

The subjects in this study will be picked from among volunteers coming from the different urban poor barangays or villages in Metro Manila. Subjects will be screened using a questionnaire as to their monthly family income, lifestyle, and past medical history (see Annex). They will also be stratified according to age and sex.

The inclusion criteria are the following:

1. Age range: 15-50 years old, male or female, with 15 subjects for each age range of 5, or a total of 210 subjects, 105 for each sex. Females should be non-lactating, pre-menopausal.

2. No history of chronic intake of drugs such as steroids, oral contaceptives, hormonal replacement therapy, thyroxine therapy, anti-thyroidal drugs, anti-convulsants.

3. No underlying illnesses, such as diabetes mellitus, thyroid and parathyroid disorders, other endocrine disorders, malignancies, renal failure, renal tubular acidosis, liver disease.

4. Non-alcoholic, defined as at least weekly alcohol binges to the point of intoxication.
Non-smoker, defined as habitual consumption of cigarette.

5. No history of fracture.

6. Estimated monthly family income should not be more than P5,000.00, the poverty line set by NEDA (National Economic Development Authority).

Pertinent history-taking and physical examination to rule out above conditions will be done. An informed consent will be obtained. The patient will also be asked to fill in a 3-day diet diary. The following information will also be obtained from the patient: average daily intake of calcium rich food, type of daily activities indulged in, regular exercise, if any.

2.C. LABORATORY METHODS

i. DEXA

A LUNAR DPX-L Dual Energy X-ray Absorptiometry machine will be used. Briefly, an X-ray source from the machine emits two beams of photons at two different energies which pass through the limb to be studied. After differential absorption of the two photons of energy by bone and soft tissues, the transmitted radiation is then measured using a NaI scintillation counter, allowing the total bone mineral content in the path of beams to be counted and expressed in g/cm^2. Patients will have an evaluation of their lumbar spine and hip bone. Total scanning time is approximately 10 minutes (5 minutes per site). Estimated radiation dose is 2 mrem [18]. Colored print-outs of the results are generated after computer processing, and this will then be interpreted by an experienced Nuclear Medicine consultant and an Endocrinology consultant.

The described method above was also similar to the method used in the previous studies [18,20,21] done in Manila using DEXA.

ii. RIA and BLOOD CHEMISTRY

A urinalysis will be done and 10 cc of blood will be extracted from the patient for biochemical examination and hormonal radioimmunoassay. The blood sample will be placed in 2 separate vials, centrifuged, sent to the research laboratory for biochemistry examination. Biochemical parameters to be obtained are: Fasting blood sugar, serum creatinine, alkaline phosphatase, transaminases, serum potassium, serum ionized calcium and phosphorus. Colorimetric method will be used for biochemistry, using the Milton Roy Spectronic 21 machine. Serum ionized calcium will be determined using a Model 634 Ciba Corning analyzer. Analysis will be performed by an experienced medical technologist.

The serum sample for radioimmunoassay will be stored at -70C until sufficient samples could be pooled and analyzed using a double-run technique. A 5-well Packard Gamma counter will be used for radioimmunoassay utilizing commercial kits from Incstar and DPC. Hormonal assays of interest are: parathyroid hormone, TSH-IRMA, free T4, and osteocalcin. The tests will be performed by an experienced medical technologist assigned at the RIA Laboratory.

3. RESULTS OF RELEVANT STUDIES

Preliminary results on the study on the effect of gonadotropin releasing hormone on the BMD of pre-menopausal women, after 24 weeks of treatment, have shown that there is no significant

effect on BMD, although the sample size involved is still quite small (n=10) and recuitment of subjects is still ongoing [20]. There is no available data as of this writing as to the effect of calcitonin on post-menopausal osteoporotic women.

In the study conducted at St. Luke's Hospital by Redoblado, De Guzman, et. al. [18], the prevalence of osteoporosis in the high-risk group of women who underwent DEXA was high at 58%, while that of fractures was at 22%, reflecting the referral bias in this study population. 'It was also shown that the age-related changes in the spine and femoral neck bone mineral densities had an initial steep uprise peaking at 37 years of age before gradually declining with age (Fig. 1). Looking at site-specific relative risks, it was observed that for every 1 SD fall in the spine BMD from the peak adult bone mass, the relative risk of having either a hip or spine fracture was increased about 1.7X. For the femoral neck BMD, each 1 SD drop from the young adult value increased the risk for femoral neck fracture by about 5.8X, which was much higher than the relative risk with respect to the spine BMD. Figures 2 and 3 show the distribution of patients with spine and hip fractures according to age and site-specific bone density. In Figure 2 , spine fractures were noted to occur more between the ages 50-60 years, coincident with spine BMD levels below 1.0 g/cm^2, the fracture threshold for lumbar spine. In Figure 3, hip fracture tended to occur more frequently in the older age group between the ages 60-70 years and above with a femoral neck BMD less than 0.7 g/cm^2. From these data, a dramatic rise in the incidence of fractures at the spine and hip was demonstrable when the bone density at either site had fallen below the fracture threshold. An inverse relationship was also noted between the BMD and the number of years post-menopause, i.e. the BMD decreases as the number of years post-menopause increases.

4. PLANS FOR FUTURE WORK

The analysis of cortical bone and tooth samples will commence during the second project year. However, collection of samples will start during the first year.

Cortical bone samples about 1 cm^3 in size or about 0.5 gram in weight will be collected intraoperatively from healthy living patients who come to PGH Department of Orthopedics for internal fixation and pinning of fracture of either the femur, humerus, radio-ulna.

Tooth samples will also be collected from healthy patients who come for tooth extraction for various reasons at the U.P. College of Dentistry. Patients will be from 20-40 years old, of either sex, with no underlying illnesses, and no history of intake of medications, specified earlier in 2.B.

The bone and tooth samples will be washed with soap and water, dried, kept in dry containers and sent to the Philippine Nuclear Research Institute for processing. The specimens will be analyzed using either wet or dry-ashing and will be examined for trace element content using a Perkin Elmer Atomic Absorptiometer. The trace elements of interest are: Al, Mn, B, Cd, Ca, Zn, F, Mg Na, Sr.

REFERENCES

[1]. National Government Budget Allocation (1990), Department of Budget and Management. Budget of Expenditures and Sources of Financing, Manila (1987-1991).

[2]. Flavier, Juan, M.D. Secretary of Health. "How Sick Are We?" Department of Health. Health Intelligence Service, Manila (1994).

[3]. Philippine Health Statistics. Department of Health. Health Intelligence Service, Manila (1972-1988).

[4]. State of Health. Department of Health. Health Intelligence Service, Manila (1975-1985).

[5]. Annual Report. Internal Research Planning and Development, Phil. Gen. Hosp., Manila (1986-1993).

[6]. Menopause Clinic Admissions Logbook. Dep't. of Ob-Gyne, Phil. Gen. Hosp., Manila (1991-1994).

[7]. Undernutrition Among Filipino Children. Philippine Health Matters, Health Alert **7**(1991) 24.

[8]. Food and Nutrition Research Institute, n.d. National Nutrition Survey, Manila (1989/90).

[9]. U.N. Yearbook of National Account Statistics; Asiaweek. 15 February 1991.

[10].Household Expenditures in Percentage. Family Income and Expenditures Survey, National Statistics Office, Manila (1988).

[11].Comparison of Mean One-Day Per Capita Nutrient Intake and Percent Adequacy, 1978, 1982, 1987. Food and Nutrition Research Institute, Third National Nutrition Survey, Manila (1989).

[12].Office of Medical Applications of Research, NIH. Osteoporosis: Consensus conference. JAMA **252**(1984)799-802.

[13].Admissions Logbook, Department of Orthopedics, Phil. Gen. Hosp., Manila (1992-1994).

[14].Ross, PD, Wassnich, RD, Heilbrum, LK, Vogel, JM. Definition of spine fracture threshold based upon prospective fracture risk. Bone **8**(1987) 271-8.

[15].Hui, SL, Slemenda, CW, Johnston, CC Jr. Age and bone mass as predictors of fracture in a prospective study. J Clin. Invest. **81**(1988) 1804-9.

[16].Hui, SL, Slemenda, CW, Johnston, CC Jr. Baseline measurement of bone mass predicts fracture in white women. Ann. Inter. Med. **111**(1989)355-61.

[17].Melton, JL, Kan, S, Heinz, W, Riggs, L. Lifetime fracture risk:an approach to hip fracture risk assessment based on bone mineral density and age. J. Clin. Epidemiol. **41**(1988)985-994.

[18].Redoblado, R, Redoblado, A Jr., Tan, D, De Guzman, A. Bone density measurements of Filipino women using dual energy X-ray absorptiometry (DEXA): an epidemiological study. Manila, unpub.

[19].Gonzaga, F, et. al. Gonadotropin releasing hormone in endometriosis and its effect on bone mass density. Manila, an ongoing study.

[20].Carpio, S, et. al. Effects of hormonal replacement therapy on post-menopausal women. Manila, an ongoing study.

[21].Villaruel, C, et. al. Multicenter trial on calcitonin in post-menopausal osteoporotic women. Manila, ongoing study.

ANNEX

DETERMINATION OF PEAK BONE MASS DENSITY
AMONG RESIDENTS OF M.MANILA

NAME:_____ID. NO.___ AGE:___ []:M []:F
ADDRESS:_____WT.___kgs. HT.___cms.
TEL._____ OCC._____ MONTHLY FAMILY INCOME:_____

1.SOCIAL HX:
SMOKER:[]Y:[]N
ALCOHOLIC:[]Y: []N

2.DRUG INTAKE:

L-Thyroxine	[]Y	[]N
Anti-thyroidals	[]Y	[]N
Steroids	[]Y	[]N
Anticonvulsants	[]Y	[]N
Growth hormone	[]Y	[]N
HRT	[]Y	[]N
Oral/Depot Contraceptives	[]Y	[]N
Others_____		

3.PAST HISTORY:

Thyroid/Parathyroid	[]Y	[]N
Diabetes Mellitus	[]Y	[]N
Other Endocrine Dis.	[]Y	[]N
Asthma/Allergy	[]Y	[]N
Seizure Disorder	[]Y	[]N
Renal/Adrenal Disease	[]Y	[]N
Jaundice/Liver Disease	[]Y	[]N
Cancer	[]Y	[]N
Arthritis	[]Y	[]N
Menopause	[]Y	[]N
Lactating	[]Y	[]N
Fracture	[]Y	[]N

4.OB-GYNE HISTORY:
OB SCORE: G__P__
PMP:_____
LNMP:_____

5.DIET HISTORY:

	Day 1	Day 2	Day 3
Rice			
Meat			
Fish			
Smallfish			

	Day 1	Day 2	Day 3
Sardines			
Leafy Vegetable			
Legumes			
Soybean product			
Milk			
Cheese			
Butter/Margarine			
Icecream			

6.EXERCISE

	< 1hr./wk[]	1-2hrs./wk []	3 or >hrs./wk.[]
Aerobic dancing	[]	[]	[]
Jogging/Running	[]	[]	[]
Walking	[]	[]	[]
Playing Basketball	[]	[]	[]
Playing Volleyball	[]	[]	[]
Weightlifting	[]	[]	[]
Swimming	[]	[]	[]

7.LAB RESULTS:

FBS	_____	mmol/L	[]N	[]H	[]L
BUN	_____		[]N	[]H	[]L
CREAT.	_____		[]N	[]H	[]L
ALKALINE PHOS.	_____		[]N	[]H	[]L
ALT	_____		[]N	[]H	[]L
AST	_____		[]N	[]H	[]L
PHOSPHORUS	_____		[]N	[]H	[]L
POTASSIUM	_____		[]N	[]H	[]L
IONIZED CALCIUM	_____		[]N	[]H	[]L
TSH-IRMA	_____		[]N	[]H	[]L
FREE T4	_____		[]N	[]H	[]L
PTH - N	_____		[]N	[]H	[]L
OSTEOCALCIN	_____		[]N	[]H	[]L
8 a.m. CORTISOL	_____		[]N	[]H	[]L

7.DEXA MEASUREMENTS

BMD values (g/cm^2)

A.L2-L4 _____

B.Femur:

Neck _____

Ward's _____

Trochanter _____

Total Body _____

Fig.1 Spine & Femoral Neck BMD in relation to Age

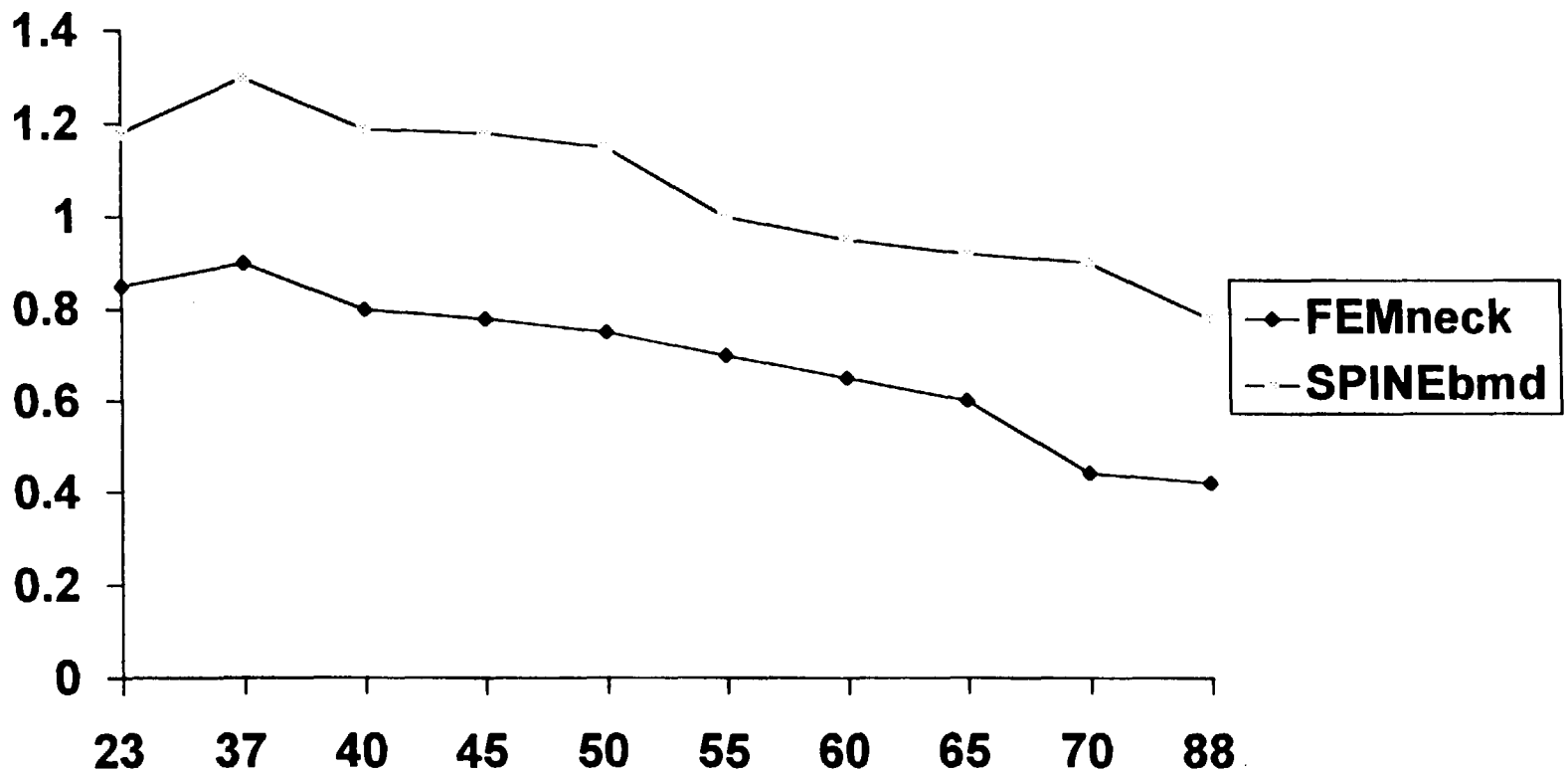

Fig 2. Distrib. of spine fracture accdg. to age and spine BMD

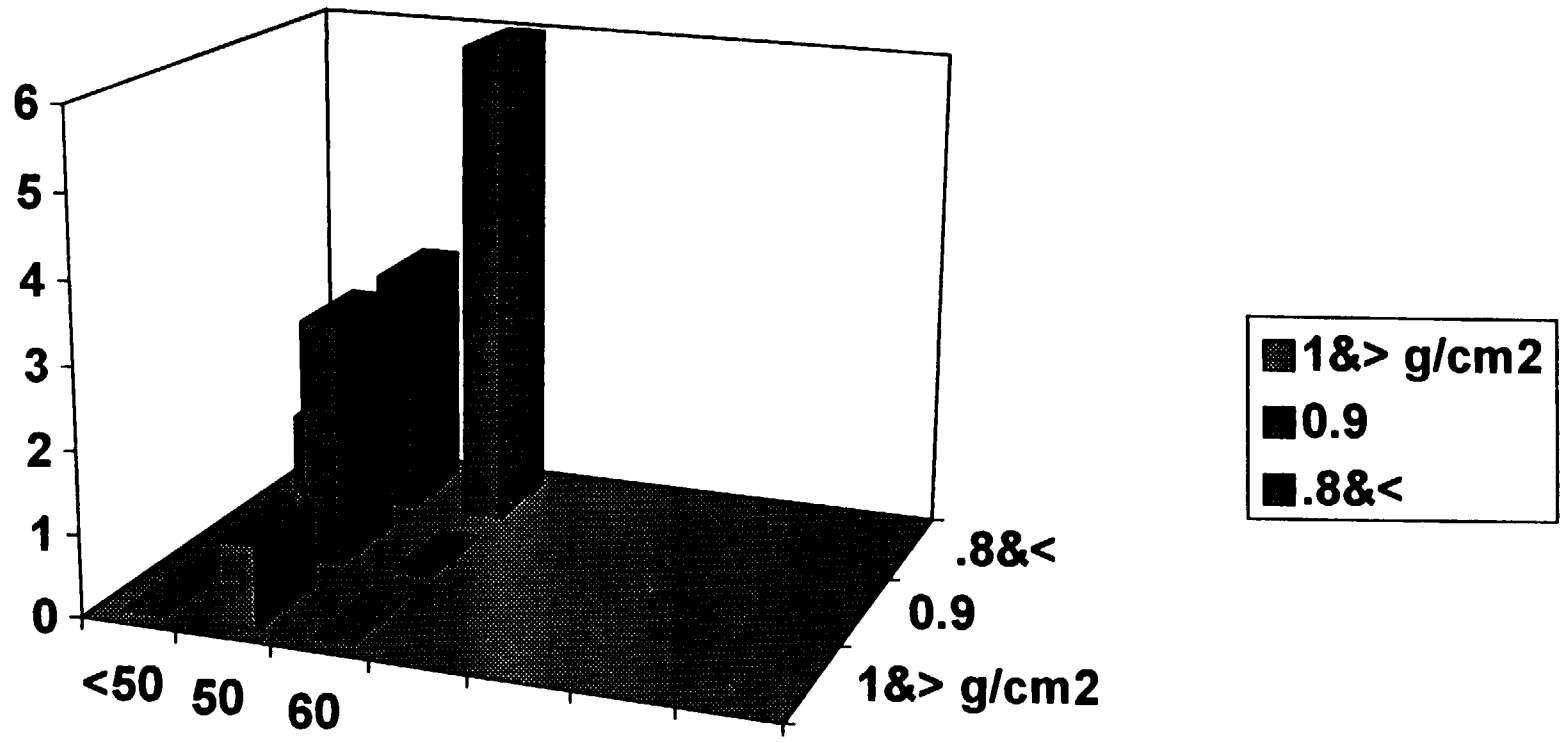

Fig. 3. Distrib. of hip fracture accdg to age and Fem. neck BMD