

**NATIONAL INSTITUTE OF TRAUMATOLOGY & ORTHOPAEDIC REHABILITATION
SHER-E-BANGLA NAGAR, DHAKA 1207
BANGLADESH**

PROJECT PROFORMA

1. Project Title : Prevalence of osteoporosis in patients of above 50 years age group attending at NITOR, Dhaka and efficacy of oral Ibandronic Acid & Coral Calcium with Vitamin D in osteoporosis
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4. Place of Study : National Institute Of Traumatology & Orthopaedic Rehabilitation (NITOR)
5. Sponsoring Collaboration Agencies : Aristopharma Ltd. 7 Purana Paltan Line, Dhaka-1000
6. Type of Study : Hospital based cross sectional study
7. Duration of Study : November 2017 to January 2019
8. Total Cost : [REDACTED] Taka
9. Date : 27 November 2017
10. Signature of Principal Investigator :
11. Signature of Co-Investigators (S) :

Prevalence of osteoporosis in patients of above 50 years age group attending at NITOR, Dhaka and efficacy of oral Ibandronic Acid & Coral Calcium with Vitamin D in osteoporosis

INTRODUCTION

The consequences of osteoporosis include the financial, physical, and psychosocial, which significantly affect the individual as well as the family and community. An osteoporotic fracture is a tragic outcome of a traumatic event in the presence of compromised bone strength, and its incidence is increased by various other risk factors. Traumatic events can range from high- impact falls to normal lifting and bending. The incidence of fracture is high in individuals with osteoporosis and increases with age. The probability that 50-year-old will have a hip fracture during his or her lifetime is 14 percent for a white female and 5 to 6 percent for a white male.

Americans is much lower at 6 percent and 3 percent for 50-year-old women and men, respectively. Osteoporotic fractures, particularly vertebral fractures, can be associated with chronic disabling pain. Nearly one-third of patients with hip fractures are discharged to nursing homes within the year following a fracture. Notably, one in five patients is no longer living 1 year after sustaining an osteoporotic hip fracture. Hip and vertebral fractures are a problem for women in their late 70s and 80s, wrist fractures are a problem in the late 50s to early 70s, and all other fractures (e.g., pelvic and rib) are a problem throughout postmenopausal years. The impact of osteoporosis on other body systems, such as gastrointestinal, respiratory, genitourinary, and craniofacial, is acknowledged, but reliable prevalence rates are unknown. Hip fracture has a profound impact on quality of life, as evidenced by findings that 80 percent of women older than 75 years preferred death to a bad hip fracture resulting in nursing home placement. However, little data exist on the relationship between fractures and psychological and social well-being. Other quality-of-life issues include adverse effects on physical health (impact of skeletal deformity) and financial resources. An osteoporotic fracture is associated with increased difficulty in activities of daily life, as only one-third of fracture patients regain pre-fracture level of function and one-third require nursing home placement. Fear, anxiety, and depression are frequently reported in women with established osteoporosis and such consequences are likely under-addressed when considering the overall impact of this condition. Osteoporosis is defined as a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture. Bone strength reflects the integration of two main features: bone density and bone quality. Bone density is expressed as grams of mineral per area or volume and in any given individual is determined by peak bone mass and amount of bone loss. Bone quality refers to architecture, turnover, damage accumulation (e.g., micro fractures) and mineralization. A fracture occurs when a failure-inducing force (e.g., trauma) is applied to osteoporotic bone. Thus, osteoporosis is a significant risk factor for fracture, and a distinction between risk factors that affect bone metabolism and risk factors for fracture must be made.

It is important to acknowledge a common misperception that osteoporosis is always the result of bone loss. Bone loss commonly occurs as men and women age; however, an individual who does not reach optimal

(i.e., peak) bone mass during childhood and adolescence may develop osteoporosis without the occurrence of accelerated bone loss. Hence sub-optimal bone growth in childhood and adolescence is as important as bone loss to the development of osteoporosis. Currently there is no accurate measure of overall bone strength. Bone mineral density (BMD) is frequently used as a proxy measure and accounts for approximately 70 percent of bone strength. The World Health Organization (WHO) operationally defines osteoporosis as bone density 2.5 standard deviations below the mean for young white adult women. It is not clear how to apply this diagnostic criterion to men, children, and across ethnic groups. Because of the difficulty in accurate measurement and standardization between instruments and sites, controversy exists among experts regarding the continued use of this diagnostic criterion. In general, it is established to use Ibandronic acid & coral calcium with vitamin D for the treatment of osteoporosis but not that much tested clinically upon Bangladeshi patients. So, the aim of this study is to see the prevalence of osteoporosis in patients of above 50 years age group attending at NITOR, Dhaka and to check the efficacy of oral Ibandronic Acid & Coral Calcium with Vitamin D in osteoporosis.

(<https://consensus.nih.gov/2000/2000osteoporosis111html.htm>)

Objectives

1. To study the prevalence of osteoporosis in above 50 years age group patients attending at NITOR, Dhaka.
2. To explore the influence of various modifiable and non-modifiable risk factor on BMD.
3. To find out the efficacy of oral Ibandronic Acid & Coral Calcium with Vitamin D in osteoporosis.

METHODS

Study location

National Institute of Traumatology and Orthopaedic Rehabilitation (NITOR), Dhaka

Study design

Hospital based cross sectional study.

Study period

November 2017 to January 2019

Sample size

Sample size is calculated to be 194 subjects assuming prevalence of osteoporosis to be 8.5% (as per seed article) at 95% confidence interval and 4% absolute allowable error. Hence for study purpose 200 subjects will be taken including both sexes who will >50 years of age with or without history of fractures. Those who with previous history of fractures, hip replacement, kyphosis or scoliosis, either currently on bisphosphonates, thyroxin, steroids, immunosuppressive therapy, antiepileptic, calcitonin or any pre-existing fracture, malignancy, stroke, hemi-paraplegia, chronic kidney disease, chronic liver disease, rheumatoid arthritis, chronic obstructive pulmonary disease, organ transplantation or bed ridden patients will be excluded from study sample.

Data collection procedure

All good clinical practice (GCP) guidelines will be followed. After taking approval from the Ethical Review Board for this study, informed consent will be obtained from all subjects. Pretested data collection sheet will be used to contain information regarding patients' demographic and clinical details and history of smoking, alcohol intake, nutritional history, possible interfering diseases and anthropometric parameters like height,

Prevalence of Osteoporosis in Patients of Above 50 Years Age Group Attending at Tertiary Level Hospitals in Dhaka

Prof. Syed Shahidul Islam

Prof. of Ortho Surgery & Academic Director, NITOR

Abstract

BACKGROUND: The prevalence of osteoporosis among the elderly population is increasing with the increasing longevity of age. As a result of the aging process, the bone deteriorates in composition, structure and function, which predisposes to osteoporosis which is a major cause for morbidity and also mortality. Early detection of Osteoporosis and appropriate timely treatment may reduce the clinical symptoms, thus reducing morbidity and improve the quality of life too. The aim of study was to assess the prevalence of osteoporosis among the patients above the age of 50 years who attended the outpatient department of a tertiary level multispecialty hospital and study the associated demographic factors.

METHODS: Data were collected on anthropometric and sociodemographic factors in 200 apparently healthy Bangladeshi adults (women = 109), above 50 years of age, in a cross-sectional study carried out at National Institute of Traumatology and Orthopaedic Rehabilitation (NITOR) in Dhaka city. Patients attended here of both sexes was included in the study. Bone mineral density (BMD) was measured by dual-energy X-ray absorptiometry at lumbar spine (LS) and both right & left femur. Individuals were classified as having osteoporosis or osteopenia based on the World Health Organization criteria of T-scores.

RESULTS: It was found that osteoporosis and osteopenia were highly prevalent in persons above 50 years (osteoporosis 35% and osteopenia 41%). More females were detected with osteoporosis (44%) and osteopenia (42.9%), while only 24.2% of the males were detected to have osteoporosis and 39.4% had osteopenia. Total 52.4 % of the patients who belonged to the age group more than 70 years had osteoporosis, whereas only 24.5% of the patients who were less than 60 years of age. Among the patients, 87.5% had either deficient or insufficient level of serum vitamin D. But, only 7% of the patients had either low or high calcium level. Positive association was found between increased age, female gender, amenorrhea, and low educational status, BMI, history of fracture, history of frequent fall, history of milk avoidance and physical activity. There was no association found between osteoporosis and serum calcium & serum vitamin D.

CONCLUSION: It was found that osteoporosis and osteopenia were highly prevalent in persons above 50 years presenting with history of fracture and frequent fall. At least 1 in 2.2 women over age 50 has osteoporosis, as is 1 in 4 men aged over 50. Therefore, both men and women require adequate measures to prevent osteoporosis during later years in life.

Outcome of Osteoporosis Management with Oral Ibandronic Acid and Oral Calcium Combined with Vitamin D

Dr. Mohammad Zakaria Hemal

Thesis for Master of Surgery (Orthopaedics)

Session: September 2017

**National Institute of Traumatology and Orthopaedic Rehabilitation
Sher-e-Bangla Nagar, Dhaka-1207, Bangladesh**

**Bangabandhu Sheikh Mujib Medical University
Shahbag, Dhaka, Bangladesh**

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**Bangabandhu Sheikh Mujib Medical University
Shahbag, Dhaka, Bangladesh**

DECLARATION OF ORIGINALITY

I hereby declare that this thesis, entitled **Outcome of Osteoporosis Management with Oral Ibandronic Acid and Oral Calcium Combined with Vitamin D** is based on work carried out by me and not presented previously for any higher degree. The research work was carried out at the National Institute of Traumatology and Orthopaedic Rehabilitation (NITOR), Dhaka under the guidance of Professor Syed Shahidul Islam, Academic Director & Professor of Orthopaedic & Spine Surgery, National Institute of Traumatology and Orthopaedic Rehabilitation (NITOR), Dhaka, Bangladesh.

Dr. Mohammad Zakaria Hemal

Resident (Phase-B)
MS (Orthopaedic Surgery)
National Institute of Traumatology & Orthopaedic Rehabilitation
Sher-E-Bangla Nagar, Dhaka-1207, Bangladesh

Dated: -----

CERTIFICATE OF ORIGINALITY

I hereby declare that the thesis entitled "**Outcome of Osteoporosis Management with Oral Ibandronic Acid and Oral Calcium Combined with Vitamin D**" being submitted by Dr. Mohammad Zakaria Hemal as a thesis for the requirement of the degree of MS (Orthopaedics) is the result of original research work. This work had been carried out under Bangabandhu Sheikh Mujib Medical University at the National Institute of Traumatology and Orthopaedic Rehabilitation (NITOR), Dhaka under my close supervision and guidance. To the best of my knowledge, the work embodied in this thesis is genuine. No part of this work has been submitted for another degree or qualification in any other institute.

I have gone through the thesis. His work is genuine and is up to my full satisfaction.

Professor Dr. Syed Shahidul Islam

Academic Director & Professor of Orthopaedic & Spine Surgery
National Institute of Traumatology & Orthopaedic Rehabilitation
Dhaka, Bangladesh

Date: -----

BANGABANDHU SHEIKH MUJIB MEDICAL UNIVERSITY

This is to certify that the undersigned have read and recommended to Bangabandhu Sheikh Mujib Medical University, Dhaka for the acceptance of this thesis entitled "**Outcome of Osteoporosis Management with Oral Ibandronic Acid and Oral Calcium Combined with Vitamin D**" submitted by Dr. Mohammad Zakaria Hemal, for the partial fulfillment of the requirements for the degree of "Master of Surgery (Orthopaedics)".

Acceptance of the thesis is approved by the Board of Examiners:

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MBBS, MS (Ortho)

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National Institute of Traumatology and Orthopaedic Rehabilitation NITOR,

Dhaka

Date of approval: 20th September, 2020

ACKNOWLEDGMENTS

All praise to my creator the almighty ALLAH (SWT), for giving me the energy and perseverance to carry out my research work with honesty.

This study was performed in the National Institute of Traumatology and Orthopaedic Rehabilitation (NITOR), during the period of November 2017 to February 2020. To accomplish this work, I have been fortunate enough to receive help from a number of people to whom I hereby wish to express my gratitude.

With humble felicitation, first and foremost, I would like to tribute my utmost respect and gratitude to my respected teacher and thesis guide Professor (Dr.) Syed Shahidul Islam, Academic Director& Professor of Orthopaedic & Spine Surgery; for his direct enthusiastic supervision, constant encouragement and valuable suggestions in conducting and preparing the thesis cases from the beginning to till completion of this thesis. His relentless & inspirational drive for research works and devotion to the subject of Orthopaedic surgery and the people of this fraternity will be the guiding star throughout my life.

I am also obliged and grateful to my respected teachers Professor Md. Abdul Gani Mollah, Director, NITOR; Prof. Dr. Monaem Hossen, Prof Dr. Shyamol Chandra Debnath, Prof. Dr. Moinuddin Ahmed Choudhury, Prof. Dr. Md. Jahangir Alam, Prof. Dr. Molla Ershadul Hoque, Prof. Dr. Abdus Salam, Professor Dr. Abdur Rob, for their valuable suggestions and guidance.

I am highly obliged to Associate Prof. Dr. Md. Wahidur Rahman, Associate Prof. Dr. Md. Mohiuddin, Associate Prof. Dr. Kazi Shamim Uzzaman, Associate Prof Dr. Aminul Haq Pathan, Associate Prof. Dr. Tofayel Ahmed, Associate Professor Dr. Rezaul Karim, Associate Prof. Dr. Md. Abdus Sabur, Associate Prof. Dr. AKM Zahir Uddin, Associate Prof. Dr. Imam Gaziul Haque for their support & guidance and to all my other respected teachers and the thesis approval committee for allowing me to carry out the study on this subject at NITOR.

I am grateful especially to my co-guide; Dr. Syeed Golam Samdani, Assistant Professor, NITOR for his great support and direction whenever I needed it.

I am also grateful to Late Dr. Sabir Reza, Dr. Swapan Kumar Paul, Dr. Subir Hossain, Dr. Jibananda Halder, Dr. Sharif Ahmed Jonayed, Dr. Selim Reza, Dr. Abdul Khaleque, Dr. Fasiul Alam - Assistant professors of orthopaedic surgery; Dr. Md. Hamidul Islam, Dr. Raquib Mohammad Manjur, Dr. Zahid Ahmad- Junior Consultants; Dr. Manos Chandra Sarker, Dr. Anonto Kumar Bhakto, Dr. OZM Dastagir, Dr. Md. Shakhawat Hossain- Registrars of NITOR; Assistant Registrars-Dr. Ripon Kumar Roy, Dr. Asim, Dr. Rajib, Dr. Aminur, Dr. Riad Mazid; and also Dr. Azad, Dr. Pavel, Dr. Shuvo Prashad, Dr. Mamun, Dr. Sarwar- Medical Officers, NITOR; Dr. Faisal (Dhaka Medical College), Mr Akter & Mr. Tonmoy (Medinova Medical Services) and other colleagues for helping me in different ways to complete the thesis in time. I am also indebted to all residents from the 1st batch of the residency program at NITOR for their kind cooperation throughout journey of this academic endeavour.

I am also thankful to my patients for co-operation during their visits, follow-ups and allowing me to use their investigation reports in this thesis work.

Finally, I am indebted to my parents and other family members whom I could not look after properly during this period.

Dr. Mohammad Zakaria Hemal

Date:

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List of Abbreviations

BBS	Bangladesh Bureau of Statistics
BMD	Bone Mineral Density
BMU	Basic Multicellular unit
BMI	Body Mass Index
DXA	Duel Energy X-ray Absorptiometry
IOF	International Osteoporotic Foundation
M-CSF	Macrophage Colony-Stimulating Factor
MRC	Medical Research Council
NHS	National Health Service
NITOR	National Institute of Traumatology and Orthopaedic Rehabilitation
NOF	Neck of Femur
Oral Ca ⁺⁺	Oral Calcium
PTH	Parathyroid Hormone
RANK	Receptor Activator of Nuclear Factor- $\kappa\beta$
RANKL	Receptor Activator of Nuclear Factor- $\kappa\beta$ Ligand
S. Ca ⁺⁺	Serum Calcium
Vit-D	Vitamin D
WHO	World Health Organisation

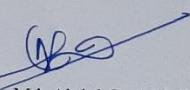
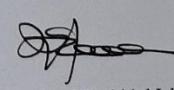
Abstract

Background: Osteoporosis and subsequent fragility fractures are on the rise with the increasing life expectancy. The effectiveness of commonly prescribed preventive medications for osteoporosis need to be studied in Bangladeshi population. **Methods:** This present quasi experimental study had been carried out among 39 osteoporotic Bangladeshi adults (women = 30, men=9) to determine the outcome of treatment with Ibandronic acid and oral calcium with vitamin-D. Patients of both sexes, with no present fragility fracture, not receiving any form of bone protective regime were included in the study. Data were collected on socio-demographic and anthropometric factors from National Institute of Traumatology and Orthopaedic Rehabilitation (NITOR) and Dhaka Medical College in Dhaka city, Bangladesh. Bone mineral density (BMD) was measured by dual-energy X-ray absorptiometry (DXA) at lumbar spine (LS), bilateral femoral necks and right distal radius as well as individual serum calcium and serum 25-OHD level were also estimated. Individuals were prescribed with monthly oral 150mg Ibandronic acid and combination of 1200mg oral calcium with 800IU Cholecalciferol/ Vitamin D3 daily in divided doses. After one year the aforementioned investigations were repeated and compared. **Results:** Among the patients, 43.6% were normal weight and 51.3% were overweight to obese. 94.9% had either deficient or insufficient level of serum 25-OHD. But, only 7.7% of the patients had low calcium level. Repeated DXA after one year or more, aforementioned treatment showed different degree of improvement in all sites most in the lumbar spine and least in the distal radius. **Conclusion:** Oral monthly 150 mg Ibandronic acid and combined oral calcium with vitamin-D showed improved BMD status at Spine and femoral necks and serum calcium and serum 25-OHD level were also improved after one year. Further study might give more insight to the matter of correction of osteoporosis and reduction of fragility fractures with such regimen.

Key words: Osteoporosis, Oral Ibandronic acid, Combined Oral calcium with Vitamin D

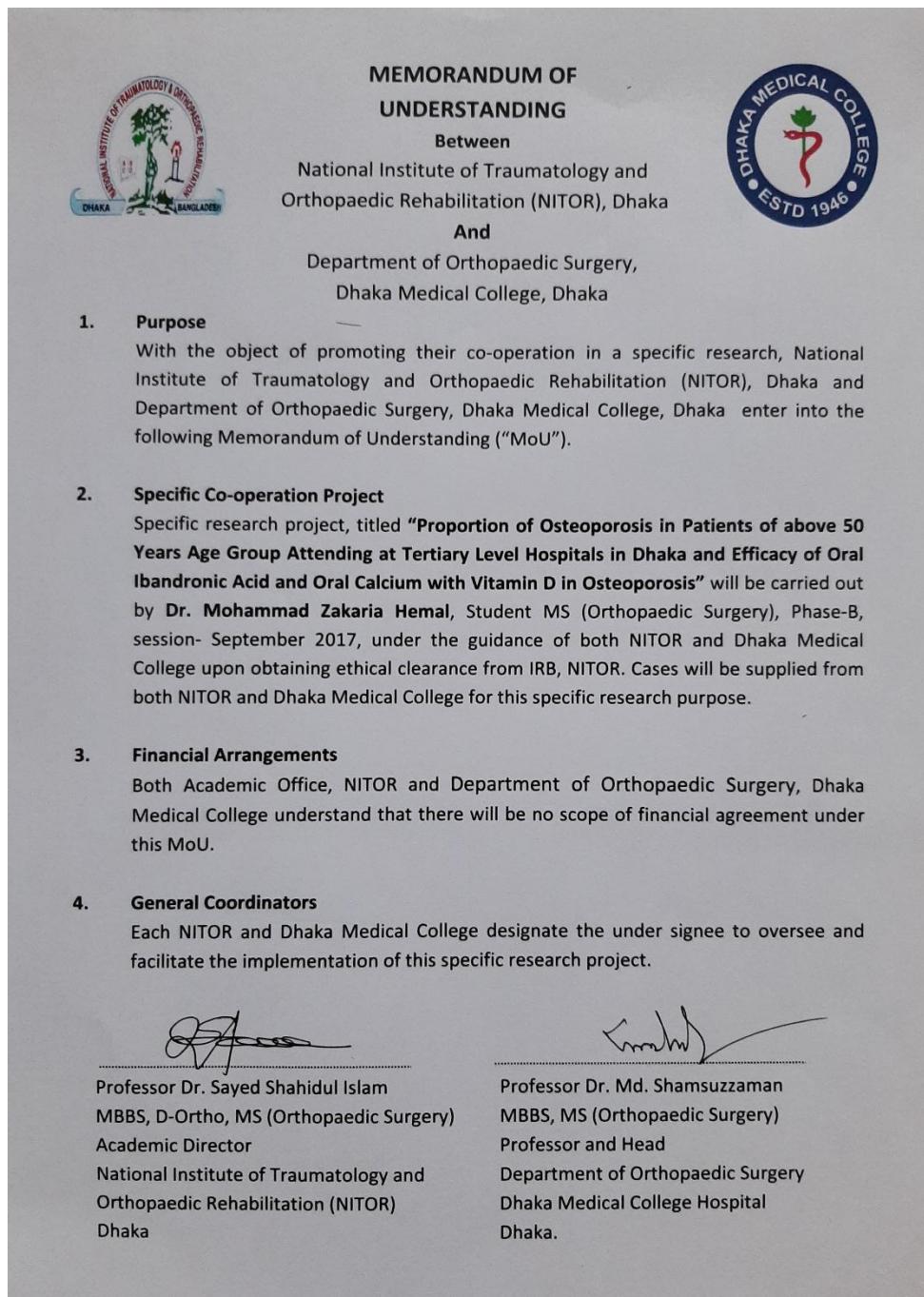
APPENDIX I

ETHICAL CLEARANCE CERTIFICATE

 GOVT. OF PEOPLE'S REPUBLIC OF BANGLADESH NATIONAL INSTITUTE OF TRAUMATOLOGY AND ORTHOPAEDIC REHABILITATION (NITOR) SHER-E-BANGLA NAGAR, DHAKA-1207, BANGLADESH 	
<p>Ref: NITOR/ACADEMY/2017/8682/A</p>	
<p>Phone : 9114075 Fax : 88-02-58152807 E-mail : nitor72@yahoo.com Url : www.nitorbd.com</p>	
<p>Date : 26/11/2017</p>	
<p><u>Institutional Ethical Review Board Certificate</u></p>	
<p>The Institutional Review Board of National Institute of Traumatology and Orthopaedic Rehabilitation (NITOR) approved the following research protocol in time.</p>	
<p>Title of the Research work : Proportion of Osteoporosis in Patients of above 50 Years Age Group Attending at Tertiary Level Hospitals in Dhaka and Efficacy of Oral Ibandronic Acid and Oral Calcium with Vitamin D in Osteoporosis.</p>	
<p>Principal Investigator : Dr. Mohammad Zakaria Hemal Student, MS (Orthopaedic Surgery), Phase- B</p>	
<p>Guide : Dr. Syed Shahidul Islam Professor of Orthopaedic surgery NITOR, Dhaka.</p>	
<p>Co-Guide : Dr. Syed Golam Samdani Asst. Professor of Orthopaedic surgery NITOR, Dhaka</p>	
<p>Place of Study : National Institute of Traumatology and Orthopaedic Rehabilitation (NITOR)</p>	
<p>Duration : November 2017 to February 2020</p>	
<p> Prof. Dr. Md. Abdul Gani Mollah Chairman Institutional Review Board (NITOR), Dhaka</p>	
<p> Prof. Dr. Syed Shahidul Islam Member Secretary Institutional Review Board (NITOR), Dhaka</p>	

APPENDIX II

Memorandum of understanding





**MEMORANDUM OF
UNDERSTANDING**

Between

National Institute of Traumatology and
Orthopaedic Rehabilitation (NITOR), Dhaka

And

Medinova Medical Services, Dhanmondi, Dhaka



1. Purpose

With the object of promoting their co-operation in a specific research, National Institute of Traumatology and Orthopaedic Rehabilitation (NITOR), Dhaka and Medinova Medical Services, Dhanmondi, Dhaka enter into the following Memorandum of Understanding ("MoU").

2. Specific Co-operation Project

Specific research project, titled "**Proportion of Osteoporosis in Patients of above 50 Years Age Group Attending at Tertiary Level Hospitals in Dhaka and Efficacy of Oral Ibandronic Acid and Oral Calcium with Vitamin D in Osteoporosis**" will be carried out by **Dr. Mohammad Zakaria Hemal**, Student MS (Orthopaedic Surgery), Phase-B, session- September 2017, under the guidance of NITOR upon obtaining ethical clearance from IRB, NITOR. Cases will be supplied from NITOR, Dhaka Medical College and CARE Medical College for this specific research purpose.

3. Financial Arrangements

Both Academic Office, NITOR and Medinova Medical Services, Dhanmondi, Dhaka understand that there will be no scope of financial agreement under this MoU. Medinova Medical Services, Dhanmondi, Dhaka will carry out about 300 cases of BMD by DXA, Serum Calcium and Serum Vitamin D free of cost for the purpose of corporate Social Responsibility and Promotion of Medical research in Bangladesh.

4. General Coordinators

The researcher will design and provide specific requisition for each case and collect report by himself or by his representative. The patients will collect report from the researcher.

Professor Dr. Sayed Shahidul Islam
MBBS, D-Ortho, MS (Orthopaedic Surgery)
Academic Director
National Institute of Traumatology and
Orthopaedic Rehabilitation (NITOR)
Dhaka

Managing Director
Medinova Medical Services,
Dhanmondi, Dhaka

APPENDIX III

Consent Form (English)

I Mr. / Mrs. hereby give informed consent willingly to participate in the study done by Dr. Mohammad Zakaria Hemal under supervision of Prof. Dr. Syed Shahidul Islam. I fully understand that my participation in the study will facilitate the generation of meaningful medical information to be useful for many others and myself in the future.

I fully understand that participation in this study will bring fruitful information for me and many others in the future.

I am convinced that during participation in the study I shall not be exposed to any physical, psychological, social or legal risks. My privacy and confidentiality will be safeguard. I would not like to be monetarily compensated because of the loss of work time. I hereby give permission to publish my photographs in any form as required. I have the right to withdraw myself from this study at any time and I shall not demand any remuneration for participation in the study.

Signature/Thumb impression:

Date:

Name of participant:

ID no:

APPENDIX IV

Consent From (in Bangla)

wPwKrmv I M‡elYv K‡g© AsMÖn‡bi m¤§wZ cÎ

GB g‡g© †NvlYv KiwQ †h Avwg

.....

wcZv/-^vgx:.....

gvZv:.....

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RvKvwiqv wn‡gj KZ...©K cwiPvwjZ M‡elYv g~jK wPwKrmv
Kvh©μ‡g Ask MÖnb Kijvg| Avgv‡K GB e‡j Avk‡Í Kiv n‡q‡Q †h,
Avgvi mswkøó wel‡qi †MvcbxqZv iÿv Kiv n‡e GB M‡elYv g~jK
Kvh©μ‡gi gva‡‡g Avgvi wPwKrmgvi cvkvcvwk weÁv‡b bZzb
AMÖMwZi m¤¢vebv i‡q‡Q e‡j Avgv‡K Rvbv‡bv n‡q‡Q| Avwg
†Kvb KviY e„wZ‡i‡K †h †Kvb mgq wb‡R‡K cÖZ„vnvi Kivi
AwaKvi msiÿY Kijvg| Avevi wPwKrmv I GB M‡elYv g~jK Kv‡R
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-^vÿi/ wUcmB

bvgt.....

ZvwiLt

wVKvbvt

APPENDIX V

Data Collection Sheet

Proportion of osteoporosis in patients of above 50 years age group attending at tertiary level Hospital in Dhaka and efficacy of oral Ibandronic Acid & oral Calcium with Vitamin-D in Osteoporosis.

A) Particulars of the patients:

1. ID No: 2. Reg. No:
3. Name:..... 4. Contact (Mob) no:
5. Address:
a) Permanent Address
.....
.....
.....
- b) Contact Address
.....
.....
.....

B) Risk Factors:

6. Age (years):.....
7. Sex: Male [1] Female [2]
8. Occupation: Farmer [1] Fisherman[2] Business[3] Service Holder[4]
 Retired [5] Housewife [6] Day Laborer [7] Others [8]
9. Education: Illiterate [1] Primary [2] SSC [3]HSC [4] Graduate [5]
 Masters [6] Others [7]
10. Weight (Kg):..... 11. Height (cm):.....
12. BMI:.....
13. History of fracture: Yes [1] No[2]

(spontaneous/Trivial Trauma;

Site, distal Radius/ Vertebral body/proximal Humerus/ Others)

- | | | |
|---|---------|--------|
| 14. History of Parent's Hip fracture: | Yes [1] | No [2] |
| 15. History of Parent's Spinal Kyphosis: | Yes [1] | No [2] |
| 16. Current excessive Smoking: | Yes [1] | No [2] |
| 17. Guocorticoids > 3months: | Yes [1] | No [2] |
| 18. Rheumatid arthritis: | Yes [1] | No [2] |
| 19. Physical work < 30 minutes/day: | Yes [1] | No [2] |
| 20. Exposure to Sunlight < 10minutes/day: | Yes [1] | No [2] |
| 21. History of avoid milk/milk product/Ca ⁺⁺ supplement: | Yes [1] | No [2] |
| 22. Alcohol 3 or more units/day: | Yes [1] | No [2] |
| 23. History of frequent fall / Apprehension of fall: | Yes [1] | No [2] |
| 24. Presence of Secondary causes: | Yes [1] | No [2] |

(Put √ mark: IDDM, Hyperthyroidism, Hypogonadism, Menopause < 45 years, Chronic Malnutrition, Mal absorption, CLD, CKD, Amenorrhea > 1 years without Pregnancy/Menopause, Oophorectomy before 50, others):

C) Lab. Investigations:

- | | | | |
|--|------------|----------------|-----------------------|
| 25. S. Calcium level:..... | Normal [1] | High [2] | Low [3] |
| 26. S. 25-OHD level:..... | Normal [1] | Deficiency [2] | Severe deficiency [3] |
| 27.a. Femoral neck BMD (T-Score):..... | Normal [1] | Osteopenia [2] | Osteoporosis [3] |
| b. Femoral neck BMD (T-Score):..... | Normal [1] | Osteopenia [2] | Osteoporosis [3] |
| 28. Lumbar Spine BMD (T-Score):..... | Normal [1] | Osteopenia [2] | Osteoporosis [3] |
| 29. Distal Radius BMD (T-Score):..... | Normal [1] | Osteopenia [2] | Osteoporosis [3] |

D) Follow up after 1 year:

(After prescribing Oral Ibandronic Acid & Coral Calcium with Vitamin D)

30. Recent fracture: Yes [1] No [2]
(spontaneous/Trivial Trauma;
Site, distal Radius/ Vertebral body/proximal Humerus/ Others)
31. S. Calcium level:..... Normal [1] High [2] Low [3]
32. S. 25-OHD level:.....Normal [1] Deficiency [2] Severe deficiency [3]
33. Femoral neck BMD (T-Score):..... Normal [1] Osteopenia [2]
Osteoporosis [3]
34. Lumbar Spine BMD (T-Score):..... Normal [1] Osteopenia [2]
Osteoporosis [3]
35. Distal Radius BMD (T-Score):..... Normal [1] Osteopenia [2]
Osteoporosis [3]

Appendix VI

Case Illustration 1

Particulars of the patient:

Case No:	16
Name:	Ful Nahar
Age:	58 years
Sex:	Female
Occupation:	House wife
BMI	26.86
Address:	Aamtoli, Rajshahi

Presenting Complaints:

1. Pain and stiffness in the left shoulder joint for 1 year.
2. Difficulty in performing daily activities.
3. H/O present Illness:

According to the statement of the patient she felt from a chair one year back on her left shoulder. Since then she has difficulty moving her shoulder. She visited local hospital and do some x-ray. They advised her some medication and exercise ensuring her there is no fracture. But pain and stiffness didn't improve. With these complaints, she came to NITOR for better management.

4. H/O past illness : Nothing Contributory
5. Family history : No history of such trauma in family
6. Socio-economics status : Belong to lower middle class
7. Immunization history : Couldn't mention
8. Personal history : married, mother of six

General Examination:

Appearance: Ill-looking	Pulse: 78 beats/min
Blood pressure: 110/70 mmHg	Anaemia: Absent
Jaundice: Absent	Oedema: Absent
Heart: No abnormality	Lungs: No abnormality Temperature: 98.4°F
Cyanosis: Absent	Other systems: No abnormality

Systemic Examination

Cardiovascular system : No abnormality detected

Respiratory system : No abnormality detected

Alimentary system : No abnormality detected

Muskulo-skeletal system :

Look- no wasting or swelling or scar seen

Feel- tenderness present

Move-marked restriction of elevation and external rotation of left shoulder

After counselling and treating her presenting complaint, she was approached about the osteoporosis screening program with explanation. She gave consent and expressed her interest to be a part of the program. Then her BMD by DXA, S. Ca ⁺⁺, serum 25(OH)D was measured. She was advised the following management. After one year the investigations are repeated.

Treatment:**Non-pharmacological**

1. Moderate weight bearing exercise
2. At least 30 min exposure to sun light in the morning

3. Sufficient protein intake
4. Safety precautions against fall
5. Avoid caffeine drink, carbonated soft drinks, quit smoking, beetle nut

Pharmacological

1. 150 mg tab Ibandronic acid per orally once monthly for 5 years, to be taken in empty stomach in the morning. Not to lie down for 1 hour after taking the drug.
2. 600 mg calcium with 400IU vit-D3 per orally daily 12 hourly after meal for twelve months.

Comparison of investigation results

Investigations	Before medication	After medication
BMD Spine (T-score)	-4.3	-3.9
BMD right hip (T-score)	-1.7	-1.4
BMD left hip(T-score)	-1.2	-1
BMD distal radius(T-score)	-3.6	-3.6
Serum Ca ⁺⁺	8.8 mg/dl	9.1 mg/ dl
Serum 25-OHD	10.90 ng/ml	28 ng/ml

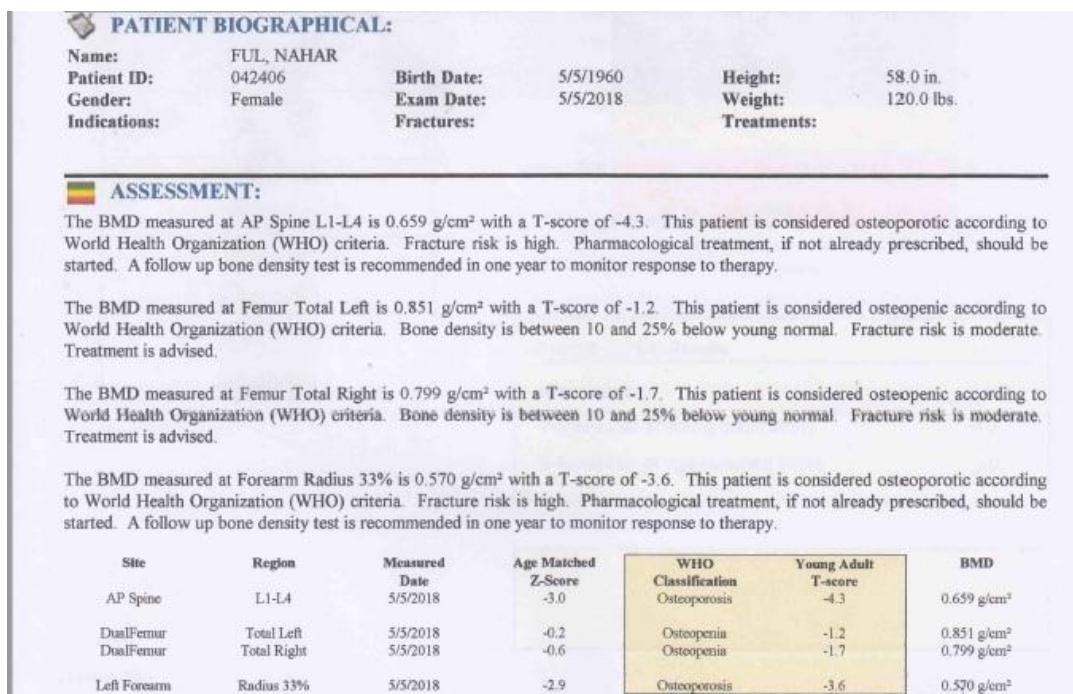


Figure I: DXA report before treatment on May 5th, 2018

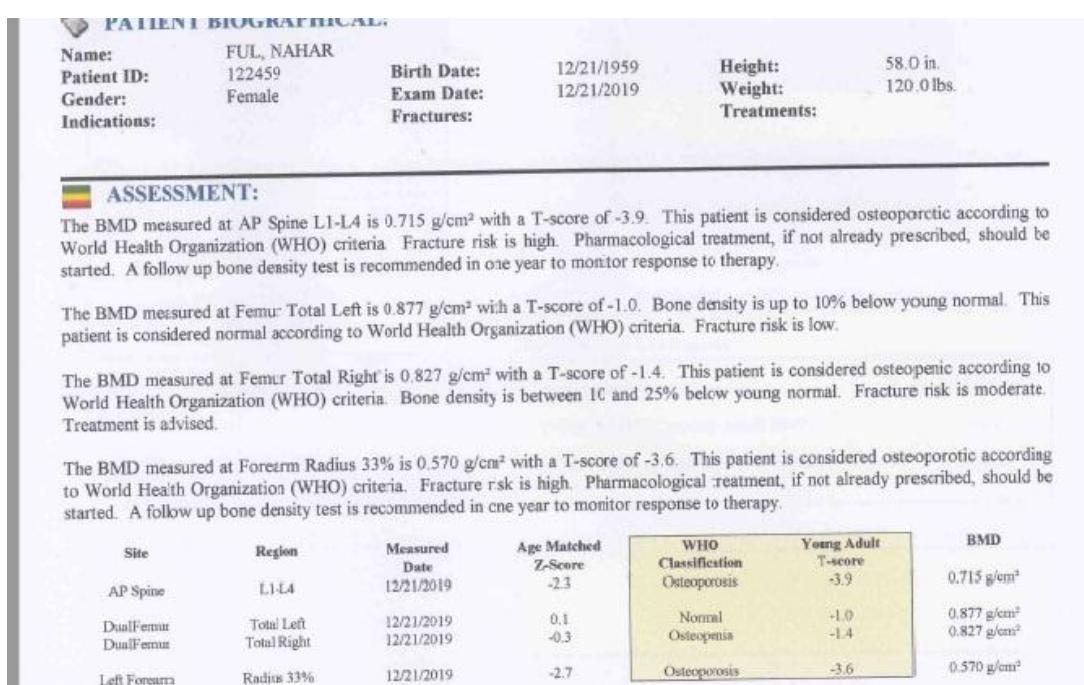


Figure II: DXA report after treatment on December 21, 2019

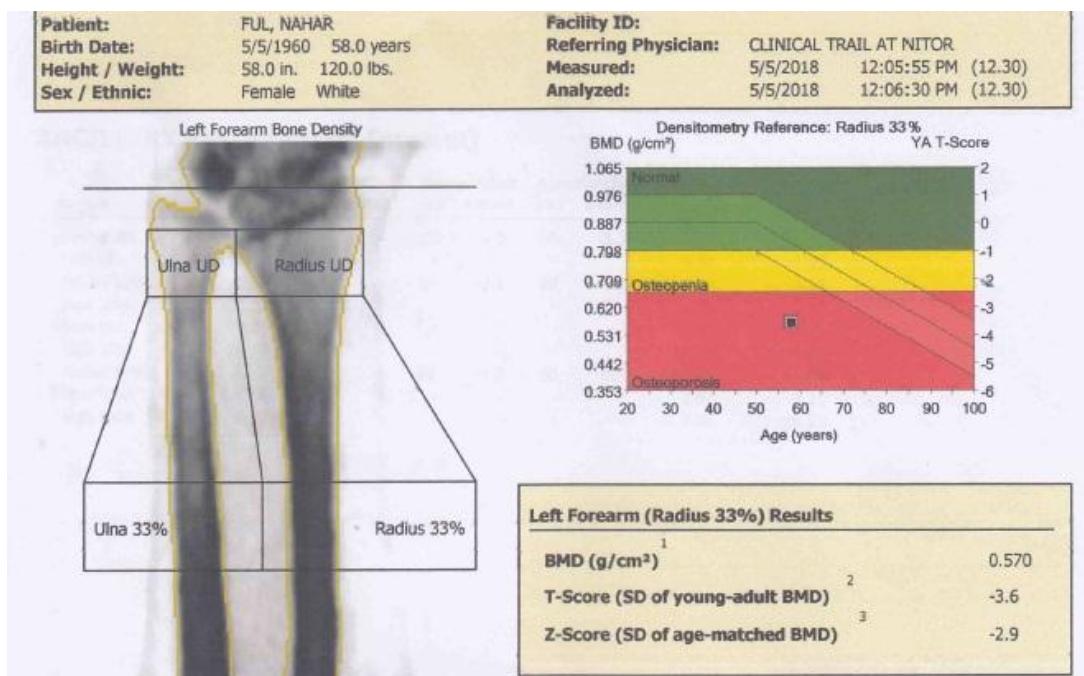


Figure III: BMD measurement at Radius before treatment on May 5th, 2018

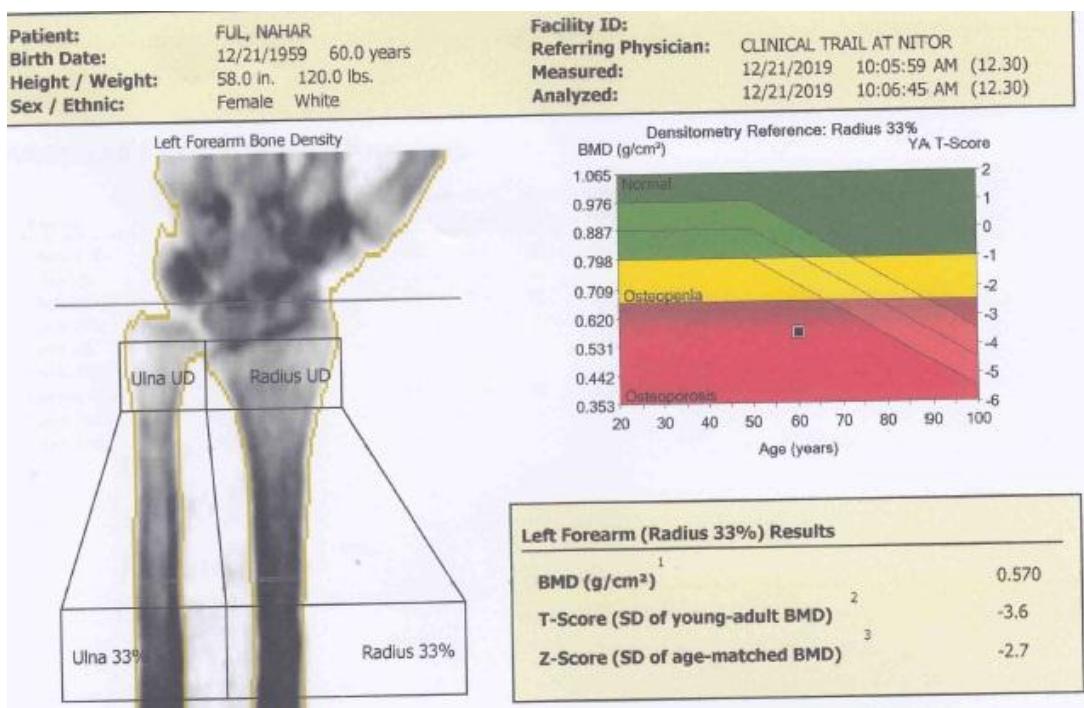


Figure IV: BMD measurement at Radius after treatment on December 21, 2019

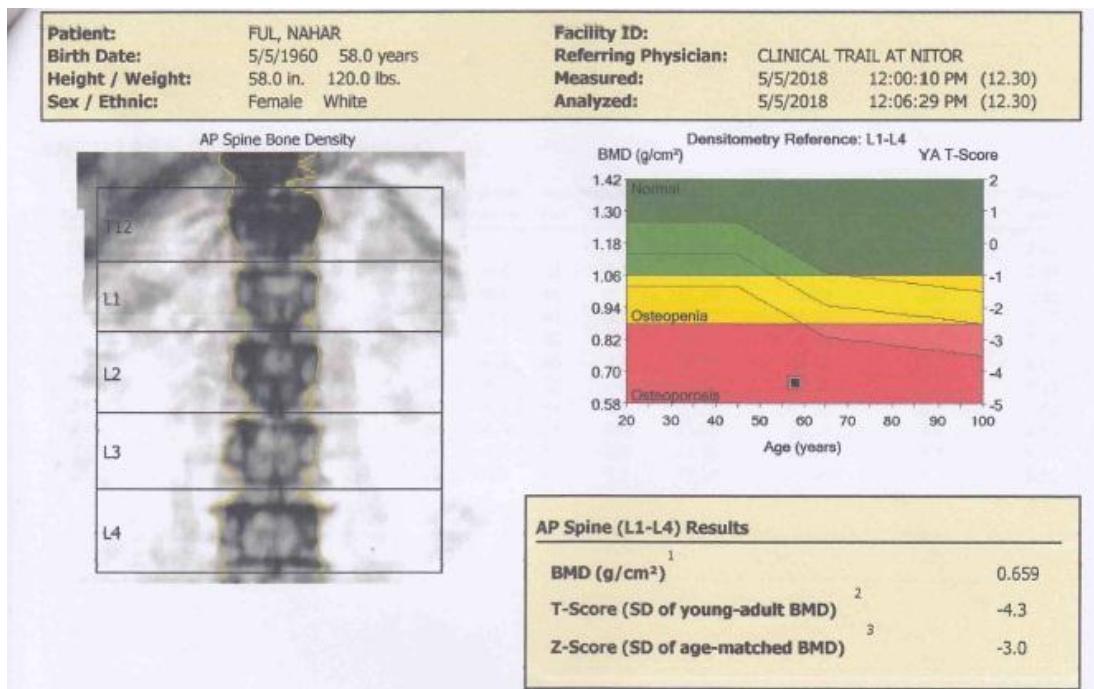


Figure V: BMD measurement at spine before treatment on May 5th, 2018

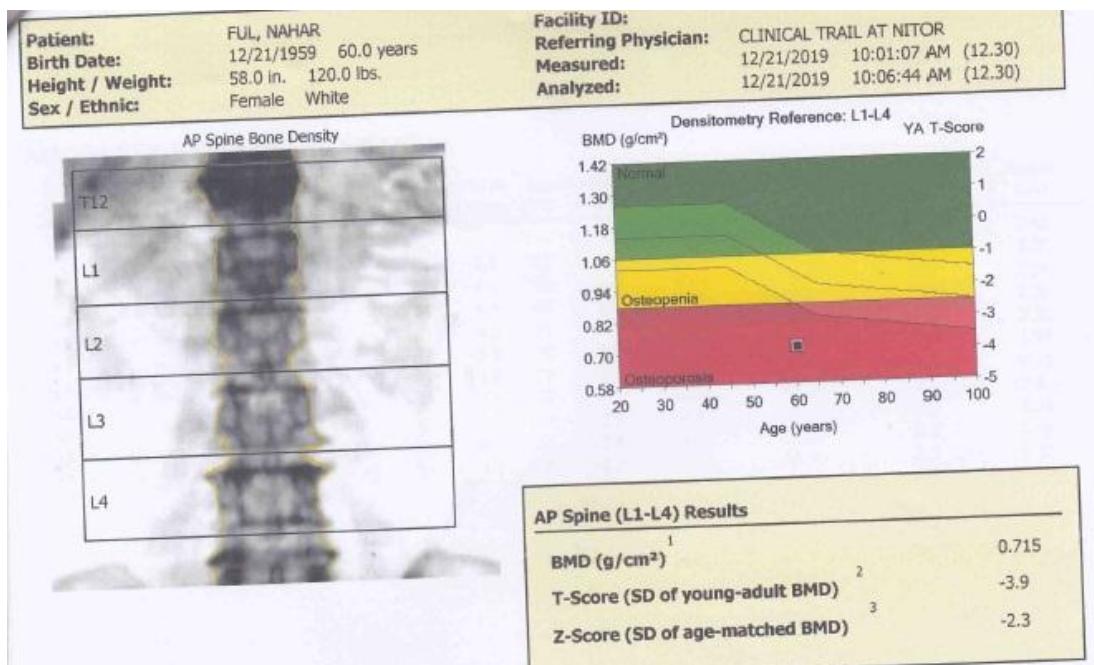


Figure VI: BMD measurement at spine after treatment on December 21, 2019

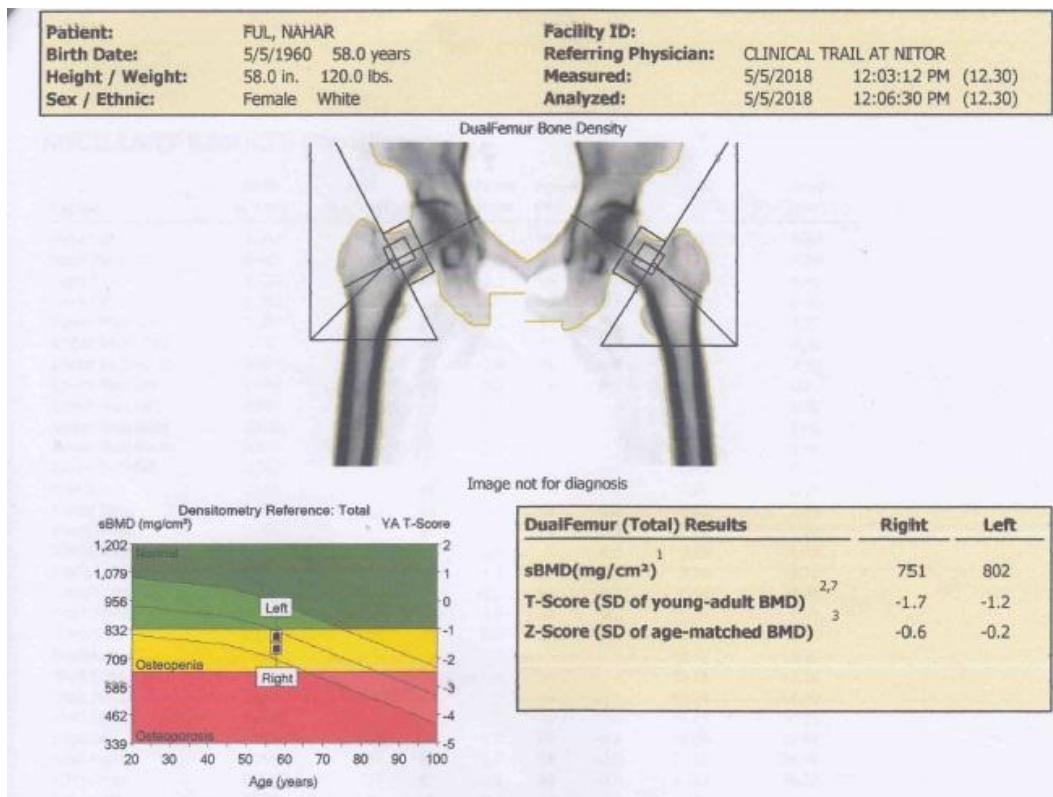


Figure VII: BMD measurement at hip before treatment on May 5th, 2018

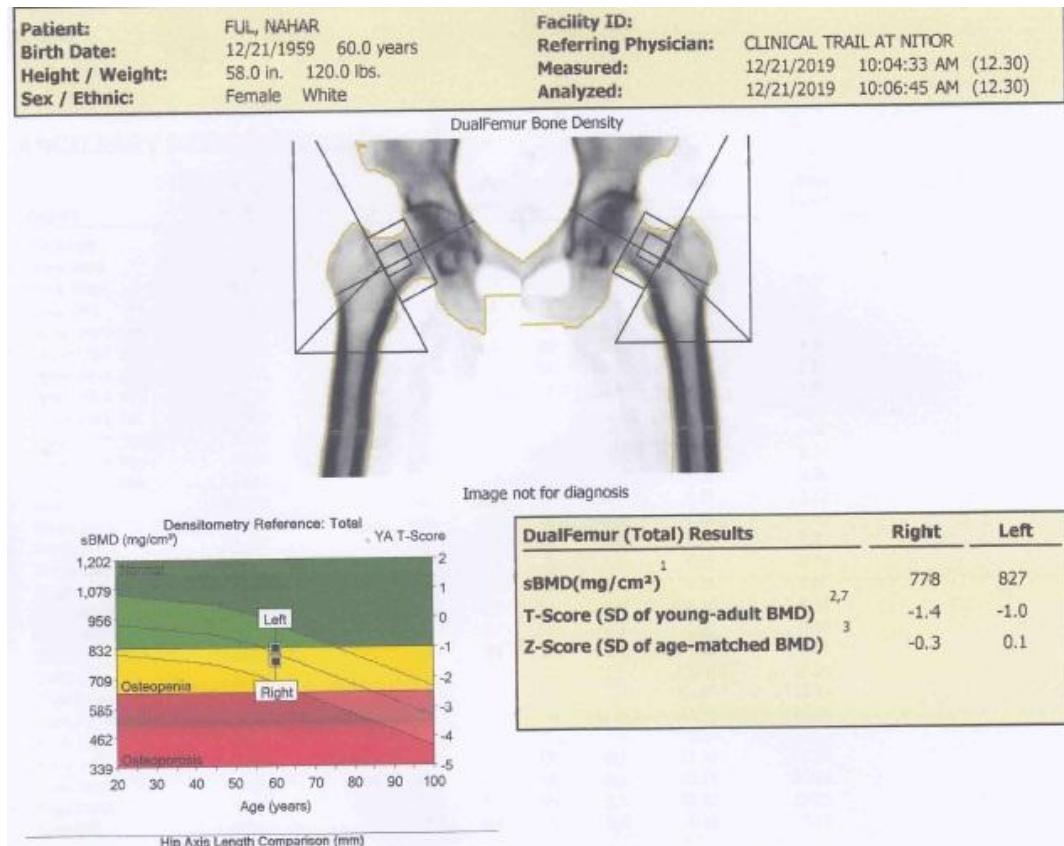


Figure VIII: BMD measurement at hip after treatment on December 21, 2019

ID No.	: D42406	Date: Sat, 5 May, 18 , 2:28:28PM
Patient's Name	: FUL NAHAR	Age : 58 Year(s) Sex : Female
Refd. By	: CLINICAL TRAIL AT NITOR (ON CREDIT)	
Specimen	: Blood	
Test	Result	Reference Value
Serum Calcium	8.8 mg/dl	Newborn: 8 - 13 mg/dL Adult : 8.4 - 10.2mg/dL Child : 10 - 12 mg/dL

Figure IX: Serum Calcium before treatment on May 5th ,2018

ID No.	: D122459	Date: Sat, 21 Dec, 19 , 12:27:29PM
Patient's Name	: FUL NAHAR	Age : 60 Year(s) Sex : Female
Refd. By	: CLINICAL TRAIL AT NITOR (ON CREDIT)	
Specimen	: Blood	
Test	Result	Reference Value
Serum Calcium	9.1 mg/dl	Newborn: 8 - 13 mg/dL Adult : 8.4 - 10.2mg/dL Child : 10 - 12 mg/dL

Figure X: Serum Calcium after treatment on December 21,2019

ID No.	D42406	Date: Sat, 5 May, 18 , 5:17:33PM
Patient's Name	: FUL NAHAR	Age : 58 Year(s) Sex : Female
Refd. By	: CLINICAL TRAIL AT NITOR (ON CREDIT)	
Specimen	: Blood	

Test	Result	Reference Value
25-OH Vitamin D	10.90 ng/mL	Deficiency : <10 ng/mL Insufficiency: 10-29 ng/mL Sufficiency : 30-100 ng/mL Toxicity : >100 ng/mL

Method: Chemiluminescent Microparticle Immuno Assay (CMIA)/ELISA.

Figure XI: Serum Vitamin D before treatment on May 5th ,2018

ID No.	D122459	Date: Sat, 21 Dec, 19 , 12:22:10PM
Patient's Name	: FUL NAHAR	Age : 60 Year(s) Sex : Female
Refd. By	: CLINICAL TRAIL AT NITOR (ON CREDIT)	
Specimen	: Blood	
Test	Result	Reference Value
25-OH Vitamin D	28.0 ng/mL	Deficiency : <10 ng/mL Insufficiency: 10-29 ng/mL Sufficiency : 30-100 ng/mL Toxicity : >100 ng/mL

Figure XII: Serum Vitamin D after treatment on December 21,2019

Case Illustration 2

Particulars of the patient:

Case No:	20
Name:	Selina
Age:	55 years
Sex:	Female
Occupation:	House wife
BMI	41.3
Address:	11/1, block-A, Nobodoy housing, mohammadpur, Dhaka-1207

Presenting Complaints:

1. Pain in the right sole for 2 weeks.
2. Difficulty in walking specially after waking up.
3. H/O present Illness:

According to the statement of the patient she stepped in a stone about 15 days back. Since then she has difficulty moving with full weight bearing on the right foot. She visited local hospital and did some x-ray. They advised her some medication and exercise ensuring her there is no fracture. But pain didn't improve. With these complaints, she came to NITOR for better management.

4. H/O past illness : Nothing Contributory
5. Family history : No history of such trauma in family
6. Socio-economics status : Belong to lower middle class
7. Immunization history : Could not mention
8. Personal history : married, mother of four

General Examination:

Appearance: Ill-looking	Pulse: 80 beats/min
Blood pressure: 140/80 mmHg	Anaemia: Absent
Jaundice: Absent	Oedema: Absent
Heart: No abnormality	Lungs: No abnormality Temperature: 98.4°F
Cyanosis: Absent	Other systems: No abnormality

Systemic Examination

Cardiovascular system : No abnormality detected

Respiratory system : No abnormality detected

Alimentary system : No abnormality detected

Muskulo-skeletal system :

Look- no wasting or swelling or scar or ulceration seen, arches are intact

Feel-Tenderness in right heel

Move-supination, pronation, inversion, eversion are normal

After counselling and treating her presenting complaint, she was approached about the osteoporosis screening program with explanation. She gave consent and expressed her interest to be a part of the program. Then her BMD by DXA, S. Ca ⁺⁺, serum 25-OHD was measured. She was advised the following management .After one year the investigations are repeated.

Treatment:

Non-pharmacological

1. Moderate weight bearing exercise and weight reduction
2. At least 30 min exposure to sun light in the morning

3. Sufficient protein intake
4. Safety precautions against fall
5. Avoid caffeine drink, carbonated soft drinks

Pharmacological

1. 150 mg tab Ibandronic acid per orally once monthly for 5 years, to be taken in empty stomach in the morning. Not to lie down for 1 hour after taking the drug.
2. 600 mg calcium with 400IU vit-D3 per orally daily 12 hourly after meal for 12 months.

Comparison of investigation results

Investigations	Before medication	After medication
BMD Spine (T-score)	-2.7	-2.4
BMD right hip (T-score)	-1.5	-1.5
BMD left hip (T-score)	-1.6	-1.4
BMD distal radius (T-score)	-2.0	-2.5
Serum Ca ⁺⁺	9 mg/dl	9.1 mg/dl
Serum 25(OH)D	11.9 ng/ml	15 ng/ml

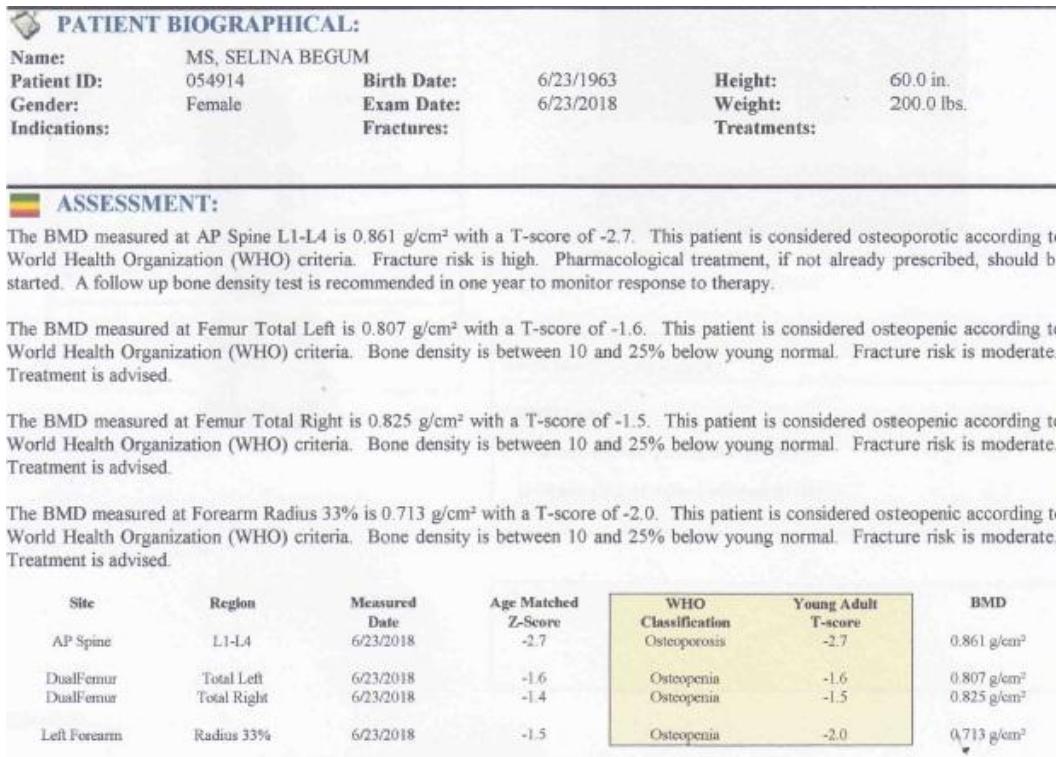


Figure XIII: DXA report before treatment on June 23th,2018

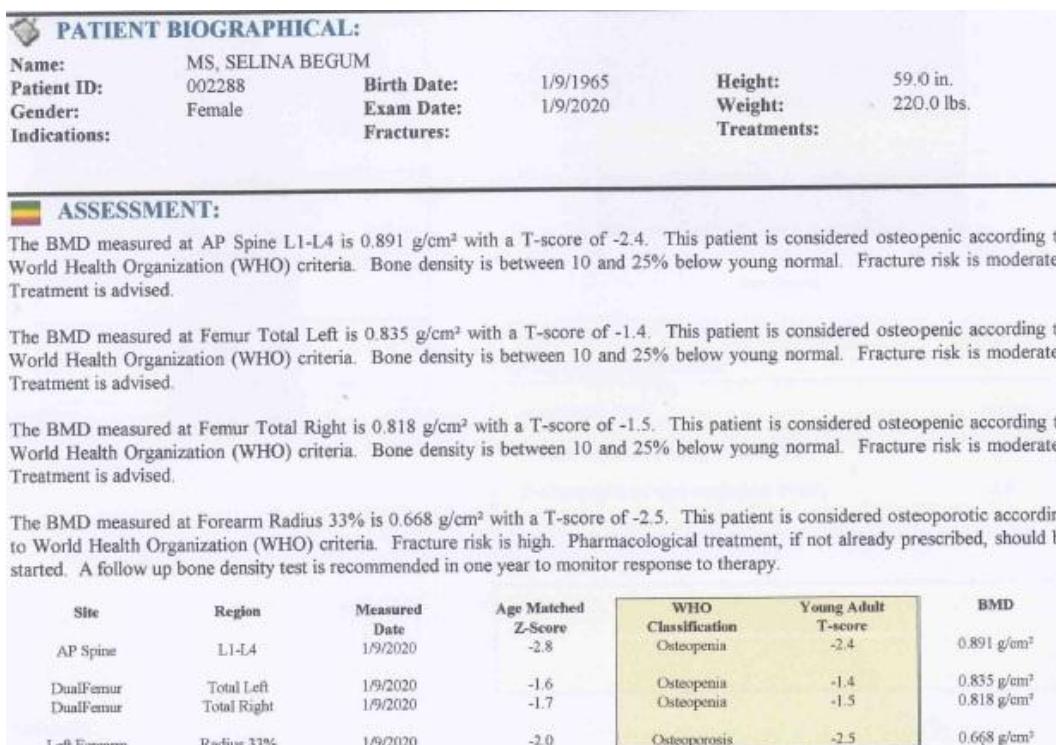


Figure XIV: DXA report after treatment on January 9th of 2020

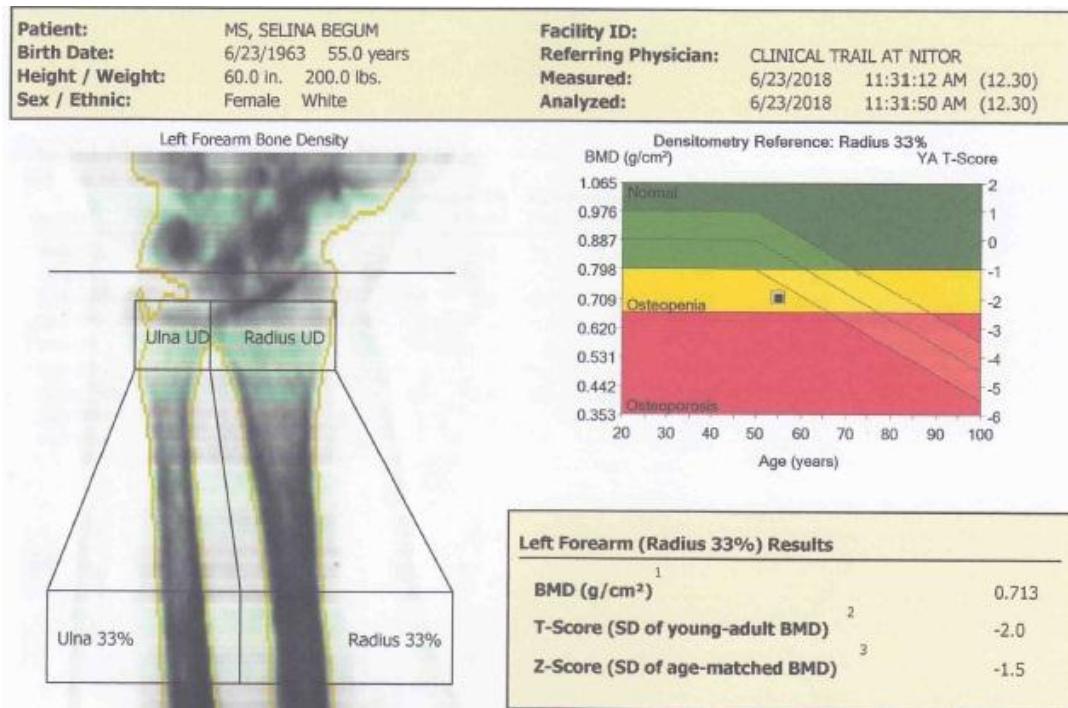


Figure XV: BMD measurement at Radius before treatment on June 23th,2018

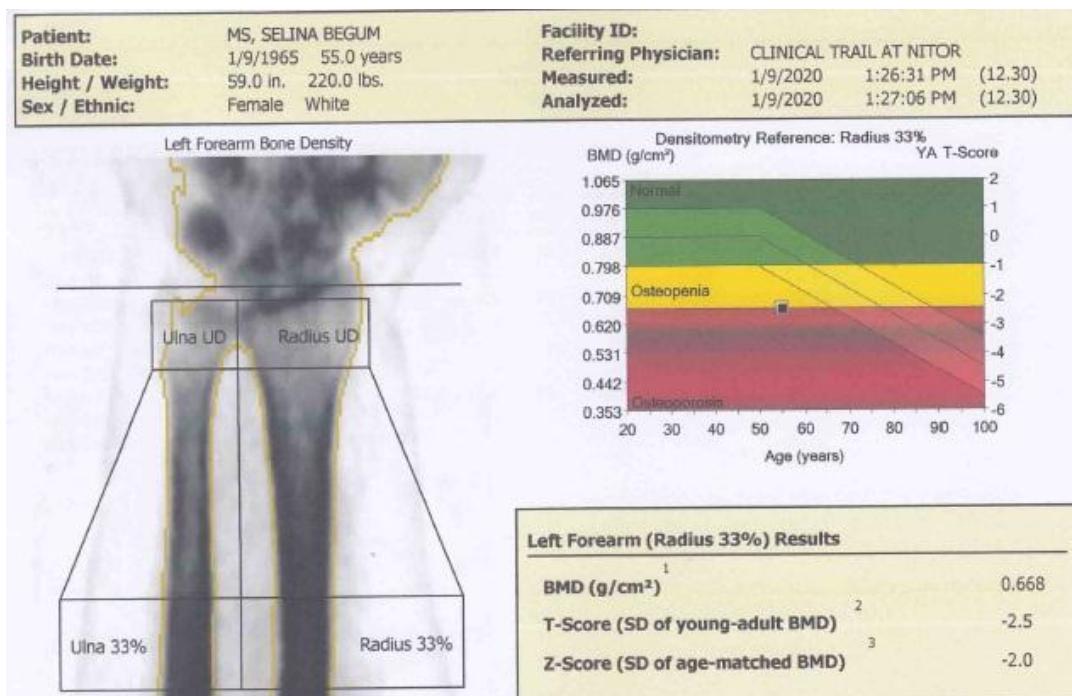


Figure XVI: BMD measurement at Radius after treatment on January 9th of 2020

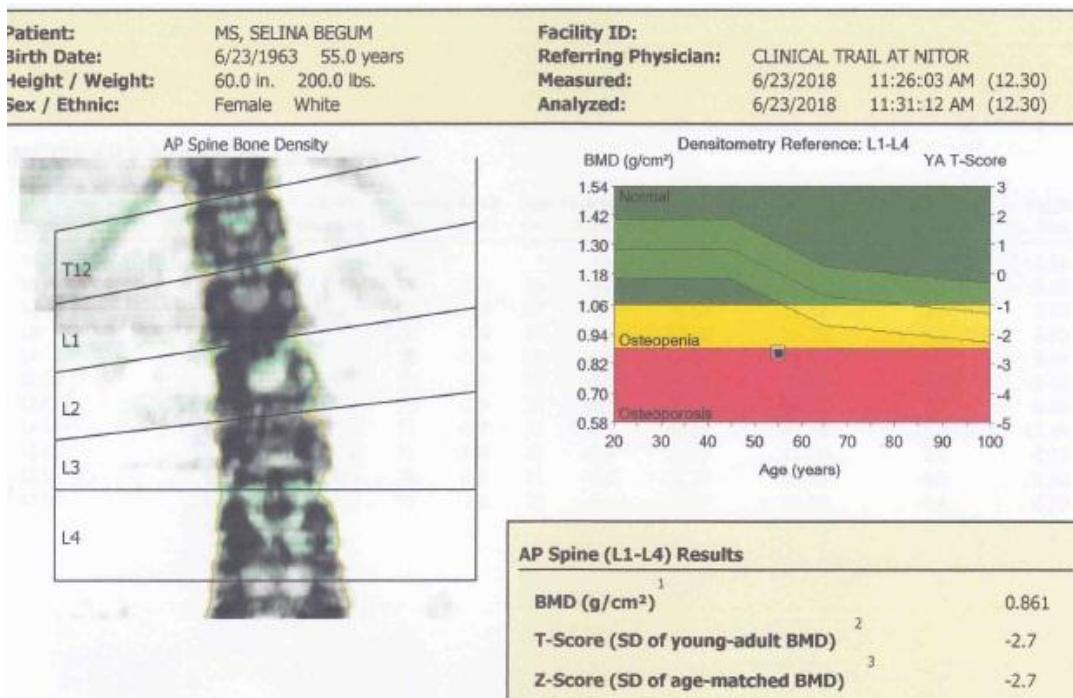


Figure XVII: BMD measurement at spine before treatment on June 23th,2018

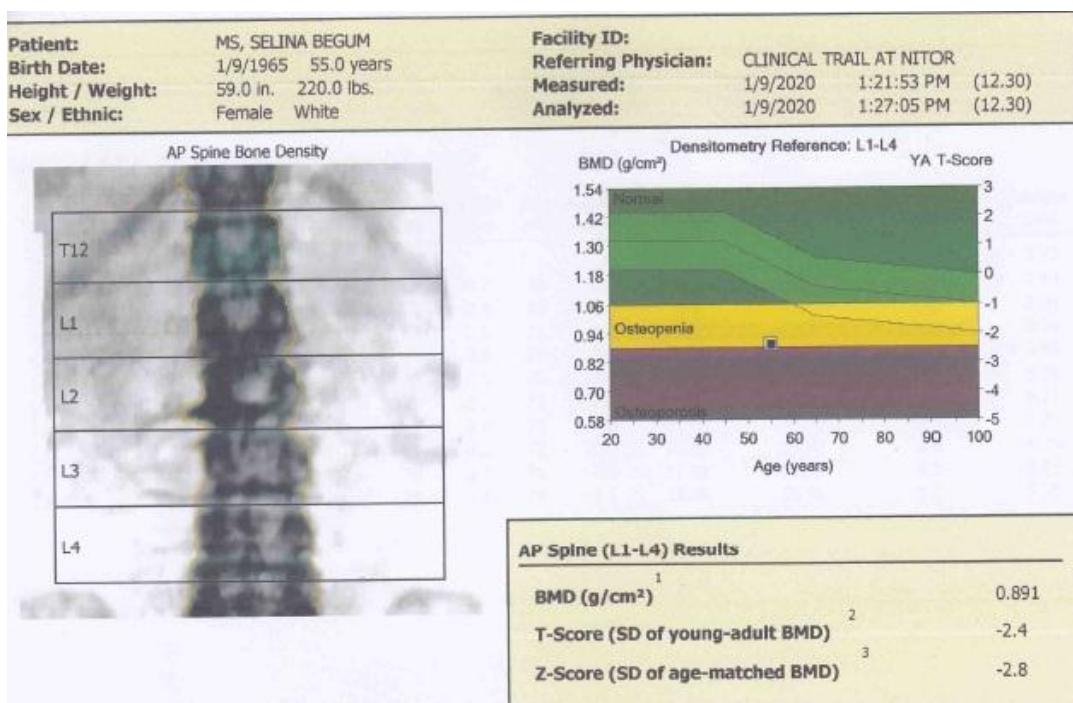


Figure XVIII: BMD measurement at spine after treatment on January 9th of 2020

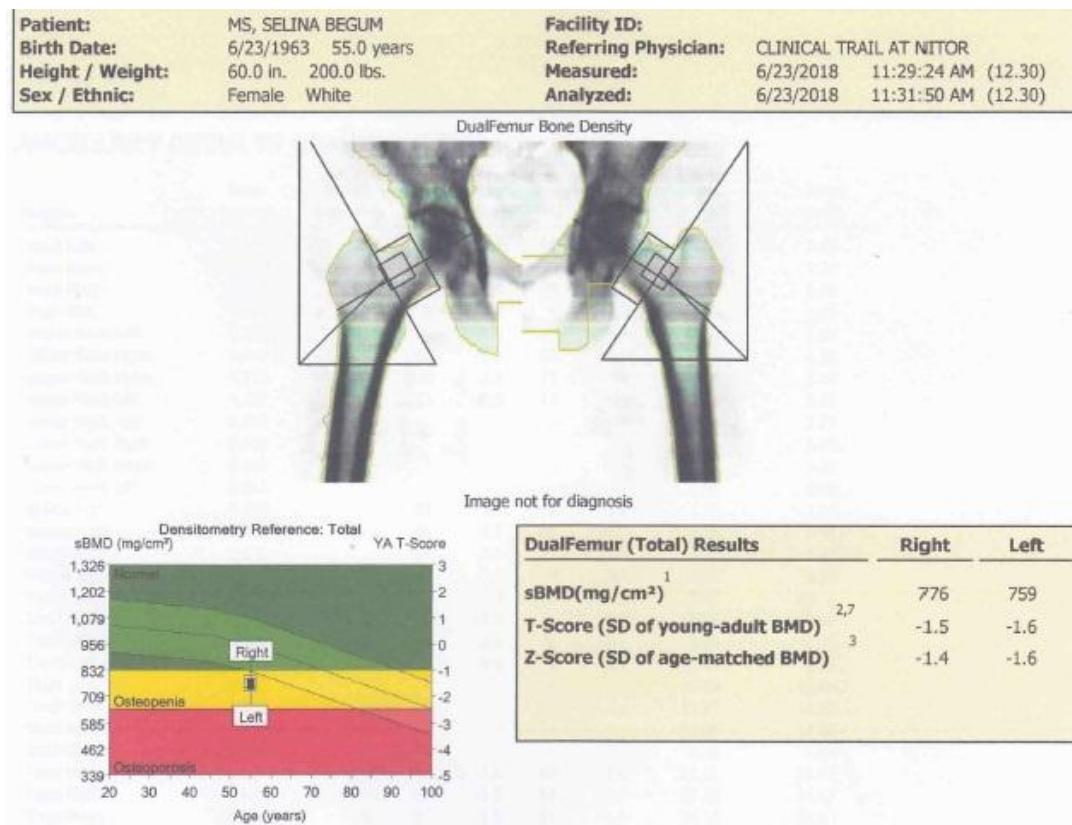


Figure XIX: BMD measurement at hip before treatment on June 23th,2018

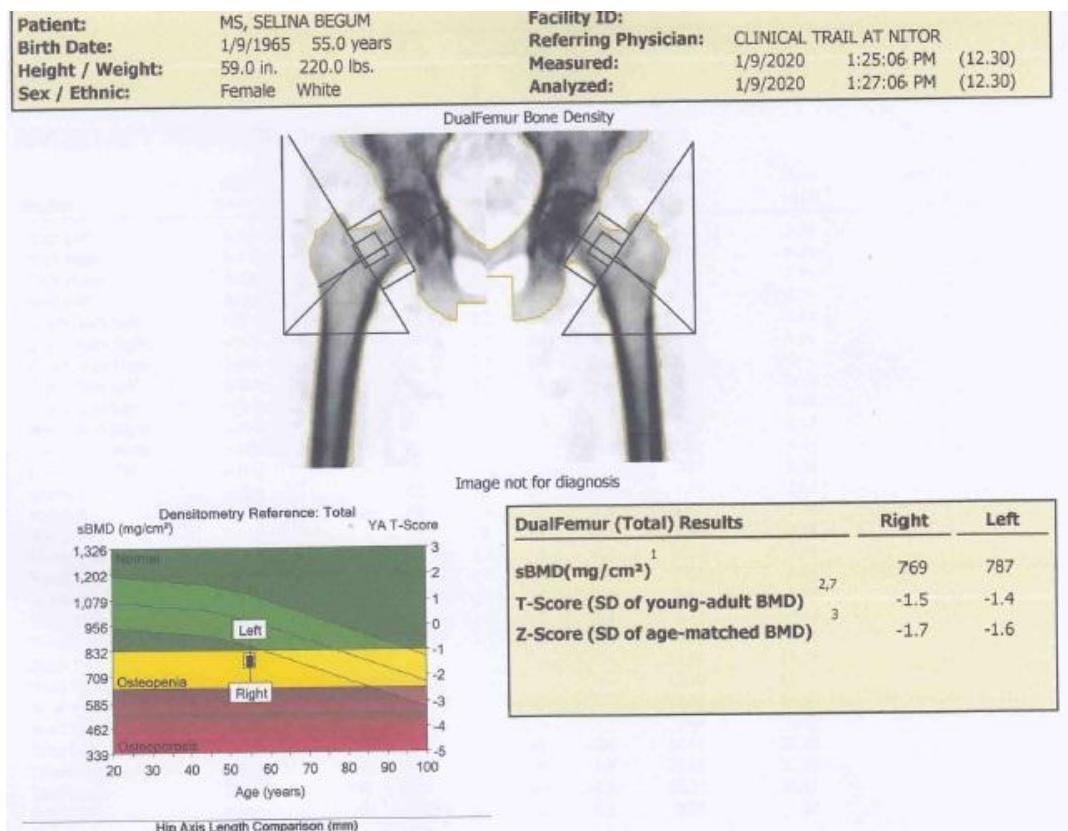


Figure XX: BMD measurement at hip after treatment on January 9th of 2020

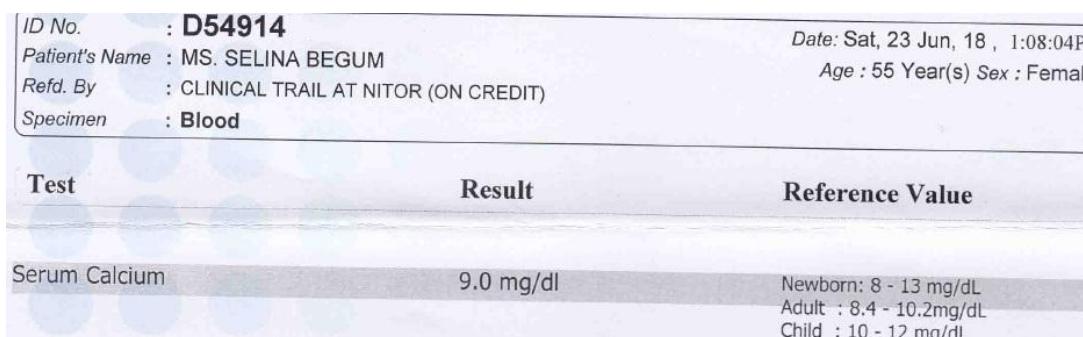


Figure XXI: Serum Calcium before treatment on June 23th,2018

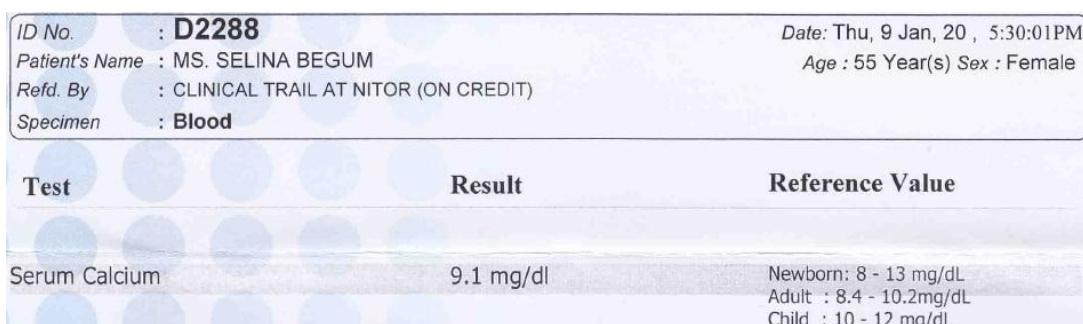


Figure XXII: Serum Calcium after treatment on January 9th of 2020

ID No.	: D54914	Date: Sat, 23 Jun, 18 , 12:38:40PM
Patient's Name	: MS. SELINA BEGUM	Age : 55 Year(s) Sex : Female
Refd. By	: CLINICAL TRAIL AT NITOR (ON CREDIT)	
Specimen	: Blood	
<hr/>		
Test	Result	Reference Value
25-OH Vitamin D	11.60 ng/mL	Deficiency : <10 ng/mL Insufficiency: 10-29 ng/mL Sufficiency : 30-100 ng/mL Toxicity : >100 ng/mL
Method: Chemiluminescent Microparticle Immuno Assay (CMIA)/ELISA.		

Figure XXIII: Serum Vitamin D before treatment on June 23th,2018

ID No.	: D2288	Date: Thu, 9 Jan, 20 , 6:43:38PM
Patient's Name	: MS. SELINA BEGUM	Age : 55 Year(s) Sex : Female
Refd. By	: CLINICAL TRAIL AT NITOR (ON CREDIT)	
Specimen	: Blood	
<hr/>		
Test	Result	Reference Value
25-OH Vitamin D	15.00 ng/mL	Deficiency : <10 ng/mL Insufficiency: 10-29 ng/mL Sufficiency : 30-100 ng/mL Toxicity : >100 ng/mL

Figure XXIV: Serum Vitamin D after treatment on January 9th of 2020

Appendix VII

Principles of DXA

A fan-beam radiation source is aimed at multiple radiation detector placed directly opposite to the site to be measured, while the patient is placed on a table in the path of the radiation beam. The source/detector assembly is then scanned across the measurement region. The attenuation of the radiation beam is determined and is related to the BMD. DXA scanners use two X-ray energies in the presence of three types of tissue -bone mineral, lean tissue and adipose tissue.

The most important informations to input in the system are the correct identification of the patient, his/her date of birth and also the sex and ethnicity which are mandatory to calculate T-scores. Sex is used by all manufacturers to calculate T-scores but all manufacturers use race in calculating Z-scores while there is inconsistency in the way race is handled when calculating the T-scores. Norland and Hologic are using race in calculating T-scores, however, GE Lunar and recent Hologic machines use the database for young normal Caucasians to calculate T-scores, regardless of the race of the subject.

A scan with correct positioning is very important and should be double checked. For the spine, the patient lies straight on the table (spine should be straight on the image), not rotated (spinous processes are centered), and centered in the field with roughly equal soft tissue fields on either side of the spine. There must be sufficient soft tissue on both sides of the spine; otherwise BMD will be under estimated. The scan should extend up sufficiently far to include part of the lowest vertebra with ribs which is usually thoracic 12th vertebra and low enough to show the pelvic brim which is usually the level of the interspace between lumber 4 and lumber 5 vertebrae. For proper

positioning of the hip, the patient should have the femur straight on the table as the shaft will be parallel to the edge of the picture, with 15–25 degree of internal rotation, which can be achieved by the use of positioning devices. This amount of internal rotation presents the long axis of the femoral neck perpendicular to the X-ray beam, providing the greatest area and the lowest bone mineral content and the lowest BMD, and is confirmed on the scan by seeing little or none of the lesser trochanter. The image should be evaluated for artifacts (e.g. surgical clips, navel rings, barium sulphate, metal from zipper, coin, clip, or other metallic object) or local structural changes as they will spuriously elevate BMD (El Maghraoui and Roux, 2008).

1. Introduction

1.1 Background of the Study

Osteoporosis may be described as “a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture” (Consensus development conference 1991, Consensus development conference 1993). The definition is later adopted by WHO in 1994 in a technical series in osteoporosis (WHO, 1994).

Osteoporosis causes more than 8.9 million fractures annually, resulting in an osteoporotic fracture every 3 seconds in the whole world (Johnell & Kanis, 2006). Most major osteoporotic fractures are associated with reduced relative survival, with an impact persisting more than five years after the index event (Bliuc, et al., 2009; Harvey, et al., 2010).

The Bangladesh Bureau of Statistics (BBS) in a population report in March 2019 showed that in 2011 there is approximately 14% women and 16% men who are 50 and above years old, which will balloon to about 26.5% & 40% for women and 24.5% & 38% for men of that age group in 2041 & 2061 respectively (Bangladesh Bureau of Statistics, 2019).

Medical treatments such as calcium and vitamin D and the oral bisphosphonates are principal components of a medical approach to help prevent osteoporotic fracture (Lin & Lane, 2004; Bogoch, et al., 2006).

Ibandronic acid shows good anti fracture efficacy in post-menopausal osteoporosis in women (Rossini, et al., 2013; McClung, et al., 2009) and also effective in male osteoporosis (Orwoll, et al., 2010; Mosekilde, Vestergaard & Rejnmark, 2013). Hip-fracture rates are reduced by 20% to 50% with bisphosphonate therapy (Varacallo & Fox, 2014).

High doses (150 mg oral monthly or intravenous equivalent) were superior to low doses (oral 2.5 mg daily) according to 1 year BMD change. (Inderjeeth, et al., 2015)

Moreover, weekly dose is associated with better tolerability and adherence versus a daily dose (Rossini, et al., 2006; Ettinger, Gallagher and MacCosbe, 2006), similarly there are studies reporting a better tolerability of monthly ibandronate versus weekly bisphosphonates (Binkley, et al., 2009; Blumentals, et al., 2009).

A meta-analysis of 29 randomized clinical trials indicated that the optimum preventive treatment of osteoporosis in more than 50 years of aged individuals are daily doses of at least 1200 mg Calcium and 800 IU of vitamin D (Tang, et al., 2007).

In a population- based intervention study it was demonstrated that Vitamin D and calcium supplementation prevents osteoporotic fractures in elderly community dwelling residents (Larsen, Mosekilde & Foldspang, 2004).

The clinical development of pharmacological agents has focused on the selection of patients on the basis of low BMD for inclusion into trials of efficacy (Holroyd, Cooper & Dennison, 2008).

1.2 Rationale of the study

Osteoporosis is a serious public health concern, affecting people worldwide regardless of gender or race, though female thought to be more affected. Osteoporotic or fragility fractures particularly of hip and spine are associated chronic disability, high dependency of the patients, increase health care costs. As there is no universal health care system established in Bangladesh, patients out of pocket expenditure is creating social disparity in receiving appropriate care. Moreover, as like other Asian counties it is suspected that Bangladeshi people have high number of vit-D deficiency and low BMI contributing to more prevalence of osteoporosis. This in time put impact on personal, social, national life through their effect of fragility fracture. Preventive medication may reduce the fragility fracture incidents and will attenuate the burden of health care cost, hospital bed occupancy, morbidity of patients and workload for surgeons and other healthcare workers. Bisphosphonates, calcium combined with vitamin shown to be helpful in this regard. Works on bisphosphonates like ibandronic acid in other parts of the world demonstrated monthly dose have similar ,if not more efficacy than daily ibandronic acid in improving BMD status and patients' compliance is better with monthly regimen. However, there is paucity of data encompassing all these issues in our country. Being the supreme research institute of orthopaedic care of the country, NITOR bears the moral obligation to the country and to her peoples to address the issue. The purpose of this study is to evaluate the outcome of treatment with 150 mg monthly oral ibandronic acid and oral Ca⁺⁺ combined with vitamin D in osteoporotic patients. This study was carried out with a view to appraise this seemingly overwhelming challenge of osteoporosis. We are sanguine that this would help persuade policy makers to take action to institute effective preventive programs for osteoporosis, as well as, instigate more health care researchers to investigate the issue.

1.3 Research Hypothesis

Monthly oral Ibandronic acid and daily divided doses of oral calcium combined with vitamin D are effective in the management of osteoporosis.

1.4 Objectives

General Objectives

1. To determine the outcome of treatment with Ibandronic acid and oral calcium with vitamin D

Specific Objectives

1. To measure the T score, serum calcium and serum 25-OHD level of the study population
2. To evaluate outcome on BMD, serum calcium and serum 25-OHD level after one year treatment with monthly 150mg oral Ibandronic acid and daily 1200mg oral calcium combined with 800 IU vitamin D

1.5 Operational definitions

The WHO classification was used for categorization of BMD

Diagnosis	T-score
Normal	>-1.0
Osteopenia	<-1.0, >-2.5
Osteoporosis	<-2.5
Severe osteoporosis	<-2.5 plus fragility fracture

(El Maghraoui & Roux, 2008).

Assessment of calcium status

Calcium status	Serum calcium level
Normal	8.4–10.2 mg/dL
Low	< 8.4 mg/dL
High	> 10.2 mg/dL

(Goldstein, 1990)

Assessment of vitamin D

Vitamin D status	Serum 25-hydroxy vitamin D level
Sufficient	$\geq 30 \text{ ng/ml}$
Insufficient	21- 29 ng/ml
Deficiency	$\leq 20 \text{ ng/ml}$

(Grant & Holick, 2005)

Improvement in T score: The improvement in T score was categorized as follows

- No improvement
- Mild improvement: The score improves up to 30%
- Moderate improvement: The score improves 31-70%
- Good improvement: The score improves $> 70\%$

2. Literature review

2.1 Historical Background of Osteoporosis

Osteoporosis has haunted women since the dawn of history. Egyptian mummies from 4,000 years ago have been found with the telltale dowager's hump. Until recently, such a posture was thought to be a frequent and inevitable consequence of a woman's aging. This assumption is evident in literature and art, which often depict women bent over with age. "Her chest had dropped, so that she stooped," noted Charles Dickens in his description of the elderly Miss Havisham in his novel Great Expectations. A striking example of a dowager's hump also appears in a painting of an old woman by the fifteenth century artist Vittore Carpa. Everything from Greek myths to classic fairy tales are peopled with stooped older women. More often than not, these depictions are probably of women with a bone thinning disease known as osteoporosis. This disease will ultimately afflict about half of all women who reach the age of sixty-five, and frequently causes the bones in the spine to collapse. Osteoporosis also affects as many as two out of every ten men over the age of seventy.

An early medical pioneer, the eighteenth century English surgeon John Hunter, described bone remodeling, which Hunter first discovered in the 1770s, was later shown to play a critical role in osteoporosis.

In the 1830s the French pathologist Jean Georges Chretien Frederic Martin Lobstein noticed that some patients' bones were riddled with larger than normal holes, and he coined the term osteoporosis (porous bone) to describe such deteriorated human bone.

In 1922 Elmer McCollum proposes, in cod liver oil there is a essential nutrient he named it vitamin D which prevents rickets in rats. From 1923 to 1925 Parathyroid hormone is

independently isolated by Adolph Hanson and James Collip and shown to boost levels of calcium in the blood. In 1930s, Hans Selye shows that small doses of parathyroid hormone foster bone formation in rats.

In 1940, Fuller Albright of Massachusetts General Hospital identified the role of oestrogen in the buildup of calcium in the bone reserve and suggested its deficit leads to osteoporosis in post-menopausal women and started treating osteoporosis with oestrogen.

In the 1960s, a Swiss physiologist by the name of Herbert Fleisch wanted to know exactly what causes calcium to be deposited in or removed from bone. In the process he discovered pyrophosphate which avidly latches onto calcium and is a principal component of bone. He eventually developed bisphosphonate drugs which suppress bone resorption by inhibiting the capacity of osteoclasts to break down bones.

In the 1990s the bisphosphonates enter pharmaceutical market as anti-osteoporosis drugs (Patlak, 2001).

2.2 Related Other Works

Due to its prevalence worldwide, osteoporosis is considered a serious public health concern. Cooper, Campion and Melton (1992) estimated that over 200 million people worldwide suffer from this disease.

Chesnut et al. (2004) in a 3 year long , randomized, double-blind, placebo-controlled, parallel-group study enrolled 2946 postmenopausal women to see the efficacy of ibandronic acid administered daily and intermittently (between-dose interval of >2 months). They concluded both group against placebo demonstrated significant and progressive increases in lumbar spine and hip BMD.

Reginster et al. (2006) in a MOBILE, a randomised, phase III, non-inferiority study over 2 years among 1609 postmenopausal women demonstrated once-monthly oral ibandronate is at least as effective and well tolerated as daily treatment and more convenient for patients with improve therapeutic adherence, optimizing outcomes.

McClung et al. (2009) in a one year, double blinded ,placebo controlled study in post-menopausal women aged 45 to 60 years demonstrated monthly 150 mg ibandronic acid prevents bone loss in post-menopausal women.

Orwoll et al. (2010)) in a one year, double blinded , randomized, placebo controlled study of men aged 30 years or more with primary, idiopathic or hypogonadism related low bone density demonstrated monthly 150 mg ibandronic acid significantly increased BMD at the lumbar spine and hip and was generally well tolerated.

Dawson-Hughes et al. (1997) found 700 IU calciferol supplementation along with 500 mg calcium, causes reduction in non-vertebral fractures in 18 months period.

Chapuy et al. (1992) using a calciferol dose of 800 IU with 1.2 g of oral daily calcium, found that hip fracture risk was reduced by 43% and non-vertebral fracture risk 32% in 18 months' time period.

2.3 Anatomy of Bone

For proper understanding of osteoporosis the anatomical organization of bone material is a must.The bone is composed mainly of in broad aspect organic materials,inorganic materials, and water.

1. Organic materials

- ✓ Collagen: Also known as osteoid before its mineralization; approximately 35% of bone weight. Mainly type 1 collagen, giving tensile strength.
- ✓ Proteoglycans: Macromolecules made up of a hyaluronic backbone with multiple glycosaminoglycans. Gives compressive strength.
- ✓ Noncollagen proteins: small amount of osteocalcin, osteonectin, osteopontin.
- ✓ Cells: Osteoblasts, osteocytes, osteoclasts
 - Osteoblasts: produce bone matrix, make type 1 collagen and other matrix proteins. Line new bone surfaces and follow osteoclasts in cutting cone.
 - Osteocytes: These are osteoblasts surrounded by their own secreted matrix. They are 90% of all bone cells. They maintain and preserve bone. They communicate with each other by their cellular processes via canaliculi.
 - Osteoclasts: Large, multinucleated cells derived from same line of cells as monocytes and macrophages. Activated osteoclasts use their ruffled border to resorb bone found in Howship's lacunae.

2. Inorganic materials

- ✓ Calcium hydroxyapatite
- ✓ Osteocalcium phosphate

They are approximately 60% of bone weight, adds compressive strength.

3. Water: Approximately 5% of bone weight varies with age and location.

All these components of bone combine to form the toughest organ of human body.

(Thompson, 2010, p. 02)

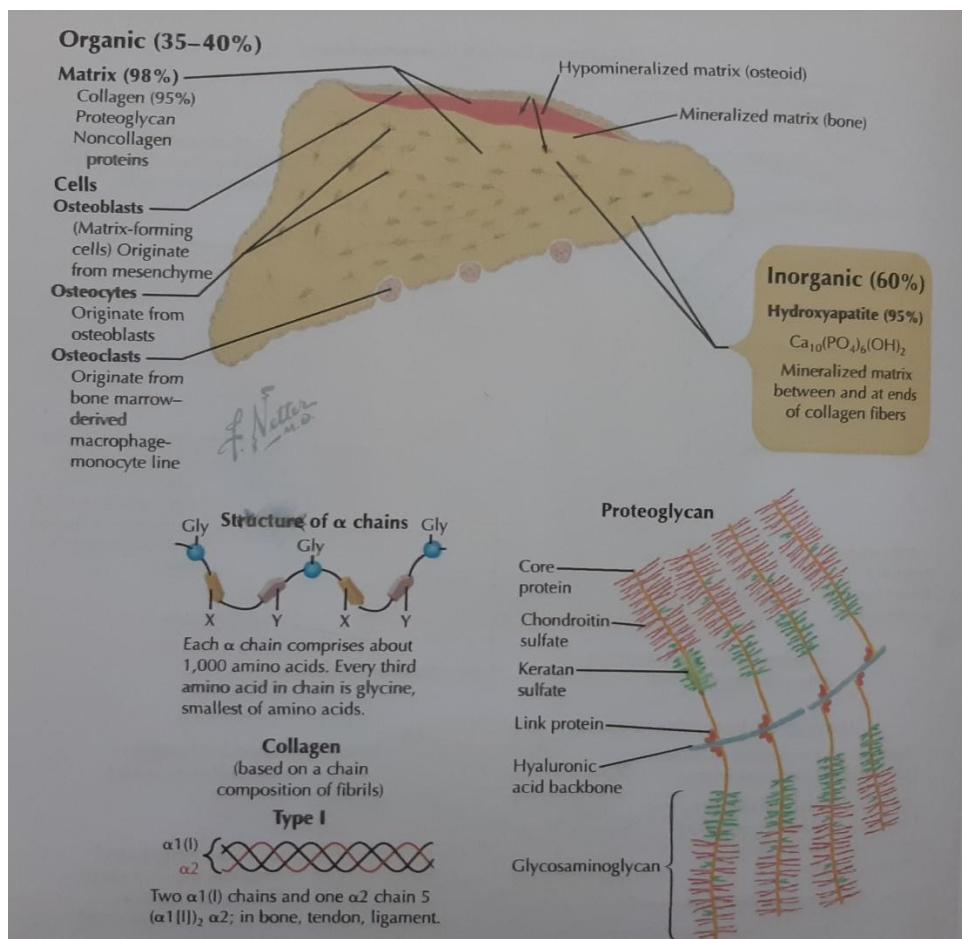


Figure 2.1: Components of Bone (Thompson, 2010, p. 02)

2.4. Pathological Anatomy

The bone tissue is constantly "turning over", allowing bone to repair and adapt to mechanical changes imposed on it. In the adult skeleton, the rate of bone turnover, collagen matrix, structure, geometry, and density together determine the bone's overall mechanical competence. Defects in these parameters can result in diseases such as

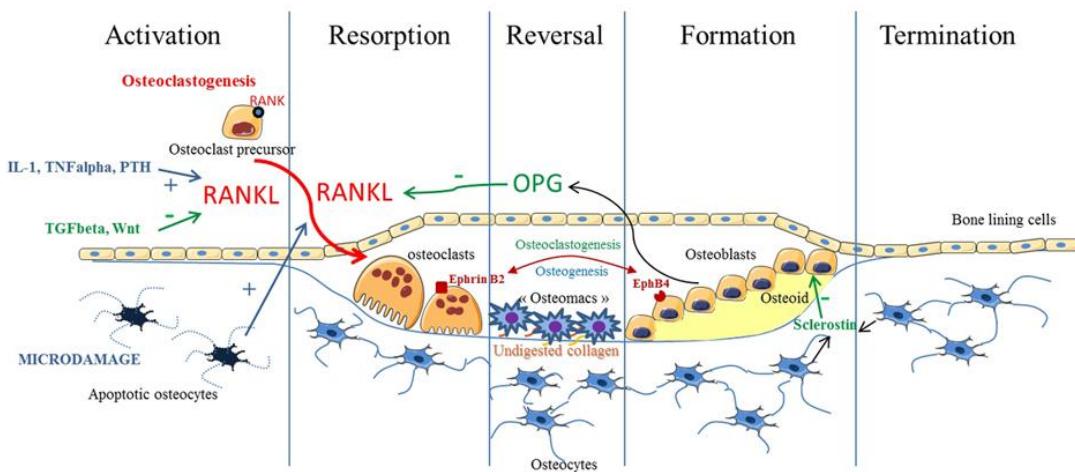
osteoporosis, osteopetrosis, osteogenesis imperfecta, and Paget's disease (Datta et al., 2008; Sims & Goi, 2008).

Tightly coupled bone resorption by osteoclasts and bone formation by osteoblasts, as well as osteocytes within the bone matrix and bone lining cells that cover the bone surface altogether known as the 'basic multicellular unit' (BMU). The BMU, through a coordinated action, is responsible for the bone remodeling. The work on the general principle, the amount of bone that is removed is to be replaced. Remodeling starts with the initiation of osteoclast formation, osteoclast-mediated bone resorption and then there is a longer reversal period of bone formation mediated by osteoblasts, followed by the full mineralization of the newly formed bone matrix (Lane & Yao, 2009).

Under the influence of parathyroid hormone, glucocorticoids or pro-inflammatory cytokines stromal cells including osteoblasts secrete the receptor activator of nuclear factor- $\kappa\beta$ ligand (RANKL), and it bind with a RANK receptor on the osteoclast precursor in the presence of a macrophage colony-stimulating factor (M-CSF). Before mature osteoclasts start to resorb bone, osteoblasts first 'prepare' the resorption site by removing osteoid from the bone surface while other matrix constituents' act as osteoclast attractors. During resorption, each osteoclast forms a sealed attachment to the bone surface where the cell membrane folds into a characteristic ruffled border within which hydrochloric acid and proteolytic enzymes are secreted. The osteoblasts and osteoclasts participating in each cycle of bone turnover work in concert, together acting as a "bone remodeling unit". Resorption and formation are coupled, the one following the another. At each remodeling site work proceeds in an orderly sequence. Prompted by the osteoblasts, osteoclasts gather on a free bone surface and proceed to excavate a cavity. After 2–4 weeks resorption ceases; the osteoclasts undergo apoptosis and are phagocytized. There is a short quiescent period, then the excavated surface is

covered with osteoblasts and for the next 3 months osteoid is laid down and mineralized to leave a new ‘packet’ of bone (or *osteon*). The entire remodeling cycle takes from 4 to 6 months. The rate may be increased or decreased either by alterations in the number of remodelling units at work or by changes in the remodeling time. During the first half of human life formation slightly exceeds resorption and bone mass increases; in later years resorption exceeds formation and bone mass steadily diminishes. . Bone depletion may be brought about by predominant bone resorption, decreased bone formation or a combination of the two. It seems self-evident that the main reason for the loss of bone strength is the reduction in bone mass. Rapid bone loss is usually due to excessive resorption rather than diminished formation, connecting trabeculae may be perforated or lost, further diminishing bone strength and increasing the likelihood of fragility fractures. Several systemic, local factors modify the procedure (Clark & Tobias, 2018).

BASIC MULTICELLULAR UNITS



(Drevelle & Faucheuex, 2013)

Figure 2.2: Bone remodeling cycle (IL: interleukin, OC: osteocalcin, OPG: osteoprotegerin, PTH: parathyroid hormone, TNF: Tumor Necrosis Factor)

2.5. Classification of Osteoporosis

The following four general descriptive categories are proposed for men and women using measurements of DXA.

- Normal. A value for BMD that is higher than 1 SD below the young adult female reference mean (T-score greater than or equal to -1 SD).
- Low bone mass (osteopenia). A value for BMD more than 1 SD below the young female adult mean, but less than 2.5 SD below this value (T score less than -1 and greater than -2.5 SD).
- Osteoporosis. A value for BMD that is 2.5 SD or more below the young female adult mean (T-score less than or equal to -2.5 SD).
- Severe osteoporosis (established osteoporosis). A value for BMD that is 2.5 SD or more below the young female adult mean in the presence of one or more fragility fractures. (WHO, 1994).

3. Methods

3.1. Study design

This was a quasi-experimental study. There was no control group.

3.2. Study place

The study was conducted in three tertiary level hospitals

- National Institute of Traumatology and Orthopaedic Rehabilitation (NITOR),
Sher-E-Bangla Nagar, Dhaka.
- Dhaka Medical College and Hospital, Dhaka

3.3. Study period

The study was conducted from November 2017 to February 2020.

3.4. Study population

Patients diagnosed with osteoporosis in the study places within the defined period were the study population.

3.5. Sample Size

Sample size calculation was as follows

$$n = \frac{(Z\alpha + Z\beta)^2 \sigma^2}{(\mu_1 - \mu_0)^2}$$

When n = sample size

Z α =Level of significance

Z_β = Power of the study

μ_0 = Mean value of lumber spine BMD T score before treatment

μ_1 = Mean value of lumber spine BMD T score after treatment

σ_0 = Standard deviation of mean value of lumber spine BMD T score before treatment

Here,

$\mu_1=2.5$, $\mu_0 = 2.7$, $\sigma_0=0.9$, $Z\alpha = 1.96$ (at 5% level), $Z_\beta =0.85$ (at 80% power), (Chesnut et al., 2004)

$$n = \frac{(1.96+0.85)^2 (0.9^2)}{(2.7- 2.5)^2}$$

$$n = 159.7$$

Therefore, the total sample size was 160. Within the time frame 43 patients full filled the selection criteria and 39 patients completed the study. So, the final sample size was 39.

3.6 Sampling technique

Purposive sampling technique was applied for this study.

3.7. Selection criteria

3.7.1. Inclusion criteria

- Patients of both sex.
- Age more than 50 years
- Diagnosed cases of osteoporosis

- Patients who gave informed written consent

3.7.2. Exclusion criteria

- History/ evidence of fragility fracture, hip replacement.
- Patients currently on bisphosphonates,
- thyroxine, immunosuppressive therapy, steroids, anti-epileptics, calcitonin, teriparatide
- Pre-existing malignancy, stroke, hemi/ paraplegia, rheumatoid arthritis, ankylosing spondylitis, chronic kidney disease, chronic liver disease, primary hyperparathyroidism, hyperthyroidism, chronic obstructive pulmonary disease, follow up case of organ transplantation or bedridden patients.

3.8. Study variables

Initial/ Baseline variable:

- Serum calcium status
- Serum 25-OHD
- Bone health status before treatment

Outcome variables:

- Primary outcome variable
 - Bone health status after treatment
- Secondary outcome variable
 - Serum Calcium level after treatment
 - Serum 25-OHD level after treatment

3.9. Study procedure

After obtaining the approval of the local ethical committee, the study was conducted from November 2017 to February 2020.

Patients were informed about the study and invited to participate. Those who met the eligibility criteria were requested to provide a written consent for their participation in the study. The purpose of the study was explained in details to the patients. Data from the patients were collected in a pre-designed data collection sheet. The patients were given full assurance on some ethical point of view that under no circumstances any part of the interview would be disclosed to any unauthorized person.

Socio-demographic data included age, sex and occupational status of the patients, patient's body mass index (BMI), history of smoking, physical activity, exposure to sunlight, milk consumption, and concomitant disease were also included.

An overnight fasting blood sample was obtained for estimation of serum calcium, 25-hydroxy vitamin D, hereafter referred to as vitamin D.

Bone mineral density (BMD) was measured using dual-energy x-ray absorptiometry (DXA) scan at the neck of right femur, neck of left femur, right distal radius and lumbar spines.

Patients who were found osteoporotic, were offered treatment with oral Ibandronic acid (150 mg) monthly with daily 1200 mg oral calcium combined with 800 IU vitamin D3 supplementation. These patients were followed up for one year. After one year serum calcium, vitamin D and BMD was measured again.

3.10. Data collection tool and technique

Data were collected by face to face interview with the help of a semi-structured questionnaire.

3.11. Data Analysis

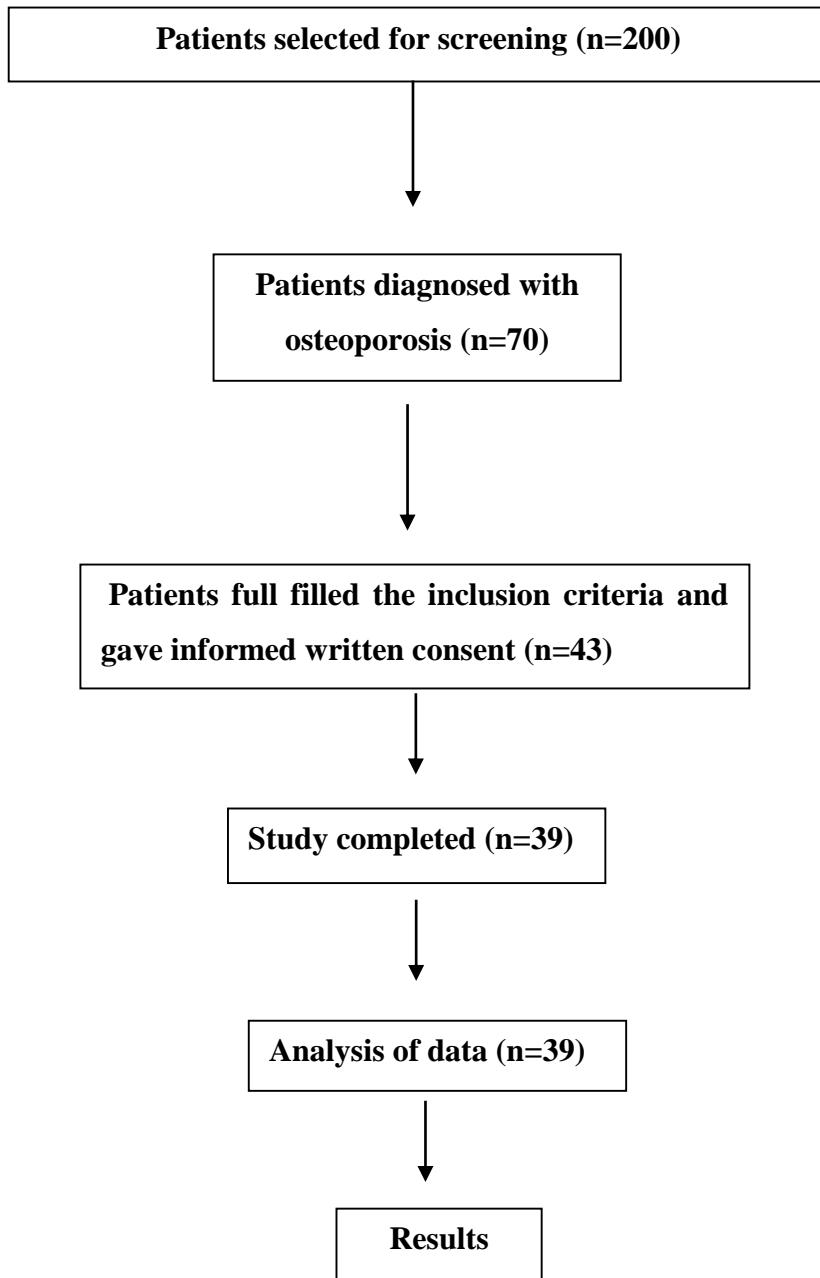
The data collected from the patients were analyzed. After completion of data collection, the data were checked and edited manually and verified before tabulation. Data were coded, entered and analyzed in a computer. The statistical analysis was conducted using SPSS (statistical package for the social science) version 25 statistical software. The findings of the study were presented by frequency, percentage in tables. Means and standard deviations for continuous variables and frequency distributions for categorical variables were used to describe the characteristics of the total sample. Associations of categorical data were assessed using Chi square test and Fisher Exact test. Associations of continuous data were assessed using paired t test where $p<0.05$ was considered significant. Here, all p-values were two sided.

3.12. Ethical consideration

Prior to the commencement of this study, the research protocol was approved by the Institutional Ethical Review Board of the National Institute of Traumatology and Orthopaedic Rehabilitation (NITOR), Sher-E-Bangla Nagar, Dhaka.

Memorandum of understanding was signed between NITOR and orthopaedic department of Dhaka Medical College and Hospital, Dhaka. Memorandum of understanding was also signed with Medinova Medical services for diagnostic facilities. The aims and objective of the study along with its procedure, alternative diagnostic methods, risk, and benefits were explained to the patients in an easily understandable local language and then informed consent was taken from each patient before been included in the study. It was assured that all records will be kept confidential and the procedure will be helpful for both the physician and patients in making osteoporosis and its risks identifiable. Also written permission was taken from the patients. The right was being given to the patients not to participate and to discontinue participation at any time in study with consideration/without penalty. Informed consent was documented properly. No financial support was taken from any organization or from the patient and no financial benefit was given to the patient for study purposes. Guidelines of research in accordance with the ethical standard responsible committee or with the Helsinki declaration of 1977 as revised in 1983 was followed.

3.13. Study flow chart



4. Results

Table I: Summary of baseline characteristics (n=39)

Baseline characteristics	Frequency (f)	Percentage (%)
Age (in years)		
50 to 59	15	38.46%
60 to 69	21	53.85%
≥70	3	7.7%
Mean ±SD	59.54 ±6.54 years	
Sex		
Male	9	23.07%
Female	30	76.93%
Body mass index (BMI)		
Under weight (<18.5 kg/m ²)	2	5.1
Normal (18.5- 24.9 kg/m ²)	17	43.6
Over weight (25.0-29.9 kg/m ²)	20	51.3
Calcium status		
Low (<8.4 mg/dl)	3	7.7
Normal (8.4 -10.2 mg/dl)	36	92.3
Vitamin D status		
Deficiency (\leq 20 ng/ml)	30	76.9
Insufficiency (21-29 ng/ml)	7	17.7
Sufficient (\geq 30 ng/ml)	2	5.1
T score		
Right hip	-1.67±0.96	
Left hip	-1.59±0.99	
Spine	-2.94±1.06	
Distal radius	-2.98±1.14	

Above table shows that the mean age of patients was 61.26 ±6.84 years, most were female. 51.3% (n=20) were overweight or obese. 92.30% (n=36) patients had normal calcium level while 76.9% (n=30) had deficient and 17.7% (n=7) had insufficient vitamin D level. Distal radius and spine were the most affected sites.

Table II: Bone health status of the patients according to measured sites (n=39)

Bone health status	Frequency (f)	Percentage (%)
Right hip	5	12.8
Left hip	6	15.4
Spine	30	76.9
Distal radius	24	61.5

Above table shows that prevalence of osteoporosis was 12.8% (n=5) at right hip while in left hip it was 15.4% (n=6). Again, in spine, the prevalence of osteoporosis was 76.9% (n=30) while in right distal radius, it was 61.5% (n=24).

Table III: Improvement of T-score of patients before and after treating with Ibandronic acid and oral calcium with vitamin D (n=39) for one year

Improvement	Right hip		Left hip		Spine		Right Distal radius	
	Frequency (f)	Percentage (%)	Frequency (f)	Percentage (%)	Frequency (f)	Percentage (%)	Frequency (f)	Percentage (%)
No improvement	14	35.9	12	30.8	11	28.2	17	43.6
Mild improvement (Up to 30%)	22	56.4	23	58.9	26	66.7	21	53.8
Moderate improvement (Up to 31-70%)	3	7.7	4	10.2	2	5.1	1	2.6
Total	39	100	39	100	39	100	39	100

Above table shows left hip demonstrates most cases of moderate improvement 10.2 %

(n=4), while mild improvement is more in spine 66.7 %(n=26) but right distal radius site shows no improvement in more patients 43.6 %(n=17)

Table IV: Comparison of T-score of patients before and after treating with Ibandronic acid and oral calcium with vitamin D (n=39) for one year

T score	Before treatment	After treatment	P value
	Mean ±SD	Mean ±SD	
Right hip	-1.67±0.96	-1.59±0.94	0.095
Left hip	-1.59±0.99	-1.54±0.95	0.335
Spine	-2.94±1.06	-2.74±0.99	0.004
Distal radius	-2.98±1.14	-2.81±1.00	0.097

Paired sample t test showed that no significant statistical difference was found in patients before and after the treatment with ibandronic acid at right hip, left hip and distal radius as $p>0.05$. Significant statistical difference was observed in T score at spine before and after the treatment with ibandronic acid ($p<0.05$) (obtained by paired t test).

Table V: Comparison of serum calcium and serum 25-OHD level of patients before and after treating with Ibandronic acid and oral calcium with vitamin D (n=39)

T score	Serum calcium	Serum 25-(OH) D
Before treatment (Mean \pm SD)	9.07 \pm 0.39	18.79 \pm 7.28
After treatment (Mean \pm SD)	9.24 \pm 0.35	21.59 \pm 6.89
P value	0.003	0.003

Paired sample t test showed that significant statistical difference was found in patients regarding serum calcium level before and after the treatment as p=0.003. Paired sample t test also showed that significant statistical difference was too found in patients regarding serum 25-OHD level before and after the treatment as p=0.003.

5. Discussion

Osteoporosis is characterized by low bone mass with micro architectural deterioration of bone tissue leading to enhanced bone fragility. This increases the susceptibility to fracture. Osteoporosis is a silent disease, reflected only in a low bone density, till a fracture occurs (Malhotra & Mithal, 2008). The primary objective of the study was to find out the outcome of osteoporosis treatment with monthly oral 150 mg Ibandronic acid and combined form of 1200mg oral calcium and 800IU vitamin D in osteoporotic patients' who attended at tertiary level hospitals. This hospital based quasi experimental study with no control group conducted among 39 adults attending National Institute of Traumatology and Orthopaedic Rehabilitation (NITOR) and Dhaka Medical College and Hospital, Dhaka.

The mean age of patients was 61.26 ± 6.84 years where majority were female 76.9% (n=30). Two fifth of the patients (43.6%) had normal body mass index (BMI) while 51.3% were overweight and obese. Most of the patients 92.30% had normal calcium status (8.4-10.2 mg/dl) while few (7.7%) had low calcium level. Sufficient vitamin D status was found only in 5.1% patients. Alkhenizan et al. (2017) assessed the relationship between vitamin D levels and BMD within the Saudi population where they reported that 17.5% had optimum level of vitamin D.

Bone health status of the patients was measured at right hip, left hip, spine and right distal radius. The prevalence of osteoporosis was found higher in spine (76.9%) followed by distal radius (61.5%). Other studies also found higher prevalence of osteoporosis for both men and women at the spine than hip (Ejaz, et al., 2012; Shetty, et al., 2014; Naz, et al., 2016; Kadam, et al., 2017). This maybe attributable to the fact that spine contains more trabecular bone than cortical bone. Trabecular bone, which

represents 20% of the total bone mass, has an accelerated metabolism and therefore a more rapid and earlier loss than cortical bone (Blumsohn, et al., 1995).

Bisphosphonates are the most commonly prescribed bone protective medication. These agents are hydroxyapatite analogues that directly deposit into bone and interfere with osteoclast bone resorptive function, and ultimately induce their apoptosis (Diab & Watts, 2013). In this study, 39 patients who were found osteoporotic were treated with oral Ibandronic acid (150 mg) monthly and oral calcium with vitamin D supplementation and were followed up for one year. Adherence to Bisphosphonates are universally poor. Poor adherence results in suboptimal outcomes in terms of fracture prevention. The main reasons for poor adherence include dosing regimen (fasting and frequency), side effects, and inconvenience (Watts & Diab, 2010).

Bone mineral density (BMD) was measured again at right hip, left hip, spine and right distal radius after one year. No improvement was observed mostly in right distal radius (43.6%) while highest number of mild improvement (66.7%) was observed in spine. In right hip 7.7% patients showed moderate improvement and in left hip 10.2% patients showed moderate improvement. Study of Bilezikian (2009) and Inderjeeth et al. (2015) also found that Ibandronic acid improved the T scores at hip. Rossini et al. (2013) reported that ibandronate has significantly more sustained vertebral and nonvertebral antifracture efficacies in women with postmenopausal osteoporosis, in comparison to those observed with other nitrogen-containing bisphosphonates. Inderjeeth et al. (2015) reviewed the efficacy, safety and adherence rates with ibandronic acids as provided by randomized controlled trial data and reported that ibandronic acids are effective in on vertebral fracture risk reduction.

Conclusion

Monthly oral 150 mg Ibandronic acid with combined daily oral 1200mg calcium and 800IU vitamin D showed improved BMD status after one year both in vertebra and femoral neck. Serum Calcium and serum 25-OHD also improved with such regimen.

Limitations of the Study

We recognize that this study has several limitations. These include---

- The follow-up period was only one year so long term outcomes could not be evaluated.
- Lack of supervised drug intake may folly the final result.
- Male and female combined study may musk the outcome of the drug treatment.

Recommendations

On the basis of the present study, it can be recommended that:

1. The results of the study can be utilized for a future large study.
2. A long term study with a large series for comparison is needed.
3. A multi-centric, control based, blinded, gender specific study should be done to validate the outcome.
4. The patients should be supported with drug reimbursement and supervised intake should be encouraged.

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Master data sheet

sl	age	sex	occupation	BMI	Ca	Vit D	T r.hip	T l.hip	T spine	T distal
1	60	Female	Housewife	26.88	9.1	19.90	-2.0	-1.7	-4.6	-3.1
2	80	Female	Others	18.70	8.3	25.90	-2.3	-2.1	-4.0	-4.4
3	64	Female	Housewife	33.57	9.0	21.90	-1.7	-1.4	-2.6	-3.7
4	66	Female	Housewife	30.88	8.8	18.06	-1.3	-.5	-1.7	-3.2
5	60	Female	Housewife	20.56	9.2	33.20	-2.0	-1.9	-3.9	-4.9
6	52	Female	Housewife	22.68	9.0	25.80	-.8	-.8	-2.5	-1.3
7	52	Male	Service Holder	22.73	8.9	19.60	-1.8	-2.1	-2.6	-2.3
8	55	Male	Service Holder	24.97	8.9	15.00	-2.5	-2.2	-2.2	-1.7
9	58	Female	Housewife	26.86	8.8	10.90	-1.7	-1.2	-4.3	-3.6
10	55	Female	Housewife	24.15	9.5	20.70	-.9	-.7	-3.2	-2.2
11	60	Female	Housewife	31.50	8.7	13.80	-1.6	-1.9	-2.5	-4.1
12	58	Female	Housewife	23.59	9.7	16.00	-1.0	-1.4	-2.4	-3.7
13	56	Female	Housewife	26.81	8.7	14.60	-2.2	-2.3	-4.2	-2.6
14	62	Female	Housewife	25.74	9.5	52.40	-.9	-.1	-3.8	-1.6
15	55	Female	Housewife	23.38	9.2	17.60	-2.1	-2.6	-2.9	-2.7
16	65	Female	Others	26.88	9.7	15.80	-1.0	-1.5	-2.6	-1.7
17	55	Female	Housewife	20.56	9.3	26.70	-1.4	-1.7	-2.6	-3.7
18	55	Male	Day Laborer	21.70	9.6	17.16	-.8	-1.1	-2.7	-2.0
19	52	Female	Service Holder	26.63	8.6	15.70	-1.2	-.7	-2.6	-1.8
20	68	Male	Retired	21.06	9.6	14.60	-1.9	-1.8	-2.8	-2.0
21	67	Female	Housewife	37.40	8.9	19.80	-.6	.2	-1.3	-2.7
22	70	Female	Others	18.47	8.8	16.80	-4.0	-3.7	-4.7	-6.0
23	54	Female	Housewife	30.84	8.7	17.20	.2	.2	-1.8	-3.2
24	75	Female	Housewife	31.76	8.3	10.40	-1.9	-3.2	-4.8	-4.7
25	55	Female	Housewife	41.13	9.0	11.60	-1.5	-1.6	-2.7	-2.0
26	55	Male	Others	23.59	9.3	20.80	-1.9	-1.1	-2.9	-2.7
27	60	Female	Housewife	24.54	9.5	14.70	-1.7	-2.1	-3.2	-2.9
28	62	Female	Housewife	28.61	9.3	16.60	-1.4	-1.0	-2.3	-3.6
29	65	Male	Retired	24.26	9.6	16.60	-1.2	-2.2	-2.7	-1.0

30	65	Female	Housewife	28.05	9.5	17.50	-2.7	-3.1	-4.0	-1.2
31	60	Female	Housewife	26.86	9.3	12.80	-3.4	-2.9	-3.8	-4.8
32	65	Female	Retired	27.45	9.5	17.40	-1.7	-1.6	-3.4	-3.1
33	60	Male	Day Laborer	20.14	8.4	20.00	-.6	.7	-3.3	-2.1
34	67	Female	Housewife	19.30	8.9	17.00	-4.7	-3.8	-4.6	-4.4
35	64	Female	Housewife	23.03	9.0	16.60	-1.5	-1.0	-1.9	-3.4
36	68	Male	Service Holder	11.37	9.1	12.57	-2.0	-1.7	-1.7	-3.0
37	65	Female	Retired	25.16	9.2	26.30	-1.3	-1.1	-2.6	3.6
38	56	Male	Service Holder	29.38	9.2	13.30	.0	.3	.5	-3.0
39	68	Female	Housewife	26.86	8.3	19.40	-2.4	-2.2	-2.9	-2.4

Data sheet after treatment

sl	Ca	Vit D	T r.hip	T l.hip	T spine	T distal
1	8.5	21.10	-1.5	-2.0	-4.0	-2.9
2	8.6	46.00	-2.2	-1.9	-3.6	-4.0
3	8.9	24.00	-1.9	-1.8	-2.8	-3.3
4	8.9	21.10	-1.1	-.5	-1.4	-3.3
5	8.9	27.00	-1.9	-1.8	-4.0	-4.9
6	9.0	23.70	-1.0	-.7	-2.3	-1.4
7	9.0	20.80	-1.8	-1.9	-2.4	-2.3
8	9.0	15.40	-2.3	-2.3	-2.6	-1.6
9	9.1	28.00	-1.4	-1.0	-3.9	-3.6
10	9.1	19.70	-.8	-.3	-2.6	-1.9
11	9.3	13.10	-1.5	-1.8	-2.2	-4.3
12	9.3	20.40	-2.0	-2.2	-3.6	-3.2
13	9.4	12.80	-2.0	-2.2	-3.7	-2.6
14	9.5	46.10	-.6	-.4	-3.5	-2.2
15	9.6	23.70	-2.0	-2.4	-3.5	-2.5
16	9.6	15.60	-.7	-1.5	-2.6	-1.8
17	9.6	21.90	-1.5	-1.8	-2.4	-2.4
18	9.6	20.30	-.8	-.8	-2.0	-2.1

19	9.7	20.70	-1.0	-.6	-1.7	-1.4
20	10.2	18.80	-1.3	-1.4	-2.6	-1.9
21	9.1	22.00	-.5	-.1	-1.4	-2.8
22	9.0	20.00	-3.7	-3.8	-4.2	-5.2
23	9.0	19.00	.1	.1	-1.7	-3.0
24	9.0	25.40	-1.7	-3.1	-3.8	-3.9
25	9.1	15.00	-1.5	-1.4	-2.4	-2.5
26	9.4	19.00	-1.7	-.9	-2.7	-2.3
27	9.5	18.00	-1.8	-1.8	-3.2	-3.3
28	9.0	16.00	-1.7	-1.1	-2.1	-3.4
29	9.7	22.00	-1.0	-2.1	-2.4	-1.1
30	9.7	16.00	-2.4	-2.7	-3.8	-1.0
31	9.2	18.00	-2.9	-2.5	-3.5	-3.8
32	9.6	21.00	-1.9	-1.4	-3.0	-3.0
33	8.9	28.00	-.5	-1.0	-3.6	-2.3
34	9.1	20.00	-4.8	-3.6	-4.4	-4.2
35	9.2	20.00	-1.3	-.8	-1.7	-3.2
36	9.3	18.00	-1.7	-1.5	-1.6	-3.1
37	9.3	22.00	-1.4	-1.0	-2.4	-3.1
38	9.7	15.60	.3	.2	.4	-2.1
39	9.1	26.90	-2.8	-2.6	-2.0	-4.0