"CORRELATION OF SERUM HOMOCYSTEINE LEVELS AND THE RISK OF OSTEOPOROSIS – A ONE YEAR HOSPITAL BASED CROSS – SECTIONAL STUDY"

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LIST OF ABBREVIATIONS

BMD	-	Bone Mineral Density
HCY	-	Homocysteine
BMI	-	Body Mass Index
DEXA	-	Dual Energy X-ray Absorptiometry
H/O	-	History of
HRT	-	Hormone Replacement Therapy
Ht.	-	Height
IP No.	-	Inpatient Number
Lt	-	Left
OP.No.	-	Out Patient Number
pDEXA	-	Peripheral Dual Energy X-ray Absorptiometry
PTH	-	Parathyroid Hormone
QCT	-	Quantitative Computerized Tomography
RA	-	Radiographic Absorptiometry
ROM	-	Range of movement
Rt	-	Right
SERM	-	Selective Estrogen Receptor Modulator
Sr No.	-	Serial Number
USG	-	Ultra Sonography
Wt.	-	Weight
AP	-	Anteroposterior

ABSTRACT

TITLE: "CORRELATION OF SERUM HOMOCYSTEINE LEVELS AND THE RISK OF OSTEOPOROSIS – A ONE YEAR HOSPITAL BASED CROSS – SECTIONAL STUDY "

INTRODUCTION:

Osteo refers to bone while porous means structure with small holes. Basically, it is the microstructural deterioration of the bone characterised by decreased in bone mineral density. This is similar to Diabetes Mellitus in a way that it silently progresses until the patient presents with the osteoporotic fracture. It is becoming the major concern in developing countries like India where it goes undiagnosed in majority of population. Osteoporosis is not limited to postmenopausal women which was earlier thought to be a part of aging. Osteoporotic fractures have caused huge financial loss by increasing the morbidity as well as the mortality. Almost 7 % of the women are dependent for their basic daily activities due to the spine, hip and distal forearm osteoporotic fractures. Most influential is the hip fracture which has decreased the expected survival by 12–20%. Moreover, in terms of financial burden, cost also changes depending upon the place whether metro city or a town or a village and type of hospital as well. Hip surgery cost around 1.5 to 2.5 lakhs in private setups while it is around 50 thousand in government hospitals. Increased levels of serum homocysteine have been found to be associated with the early start of osteoporosis. It was surprising to acknowledge that 30 to 50 % of the population which is above 60 years have increased levels of homocysteine in their plasma. Although the causes are still under study, higher risk of fracture is strongly associated with increased levels of serum homocysteine . Cardiovascular, neuronal and pathologies linked to eyes are already proven to be associated with elevated serum homocysteine levels. Folate and Vitamin B12 play vital role in the methionine metabolism and so the

homocysteine. Our target is to analyse the population with decreased Bone Mineral Density (BMD) and elevated serum homocysteine levels which may bring us to the conclusion that homocysteine is also one of the risk factors for osteoporosis.

AIMS AND OBJECTIVES:

1. To correlate bone mineral density with serum homocysteine levels.

MATERIALS AND METHODS:

A one year cross - sectional study was conducted in the Department of Orthopaedics, KLEs Dr. Prabhakar Kore Hospital and MRC, Belagavi.

80 patients presenting to OPD / IPD of Department of Orthopaedics, fulfilling the inclusion and exclusion criteria were enrolled in the study. After getting a written informed consent, the patients were subjected to DEXA scan and Serum Homocysteine levels.

RESULTS AND CONCLUSION:

Statistical analysis was done using SPSS software to assess the results. There is a negative Spearman's correlation between 'AP' spine 'T' score and serum homocysteine (-0.820). Increase in serum homocysteine levels is associated with decrease in the bone mineral density. The correlation between them is statistically significant with $p<0.05$. Linear Regression shows that, rise in the serum homocysteine levels by 12.059 mmol/L decreases the bone mineral density by one standard deviation 'AP' spine 'T' score. The negative unstandardized coefficient is statistically significant as the $p<0.05$. With consideration of Spearman's correlation and Linear Regression, raised homocysteine levels in blood can be stated as a potential risk factor for skeletal Osteoporosis. Supplementation with B12 and folate vitamins could turn around the issue of impeded bone wellbeing, osteoporosis and help in forestalling osteoporotic fractures.

KEY WORDS:

Osteoporosis, DEXA scan, Homocysteine.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF GRAPHS

LIST OF FIGURES

INTRODUCTION

'Osteo' refers to bone while 'porous' means structure with small holes. Basically, it is the microstructural deterioration of the bone characterised by decreased in bone mineral density. This is similar to Diabetes Mellitus in a way that it silently progresses until the patient presents with the osteoporotic fracture. It is becoming the major concern in developing countries like India where it goes undiagnosed in majority of population[1]. Osteoporosis is not limited to postmenopausal women which was earlier thought to be a part of aging[2]. Osteoporotic fractures have caused huge financial loss by increasing the morbidity as well as the mortality. The effect of osteoporotic fractures depends on the location of fracture. Spine in the axial skeleton while hip and distal radius in the appendicular where predominantly the osteoporotic fractures occur. Almost 7 % of the women are dependent for their basic daily activities due to the spine, hip and distal forearm osteoporotic fractures. Most influential is the hip fracture which has decreased the expected survival by 12–20%[3, 4, 5]. Moreover, in terms of financial burden, cost also changes depending upon the place whether metro city or a town or a village and type of hospital as well. Hip surgery cost around 1.5 to 2.5 lakhs in private setups while it is around 50 thousand in government hospitals[6]. Increased levels of serum homocysteine have been found to be associated with the early start of osteoporosis[7,8]. It was surprising to acknowledge that 30 to 50 % of the population which is above 60 years have increased levels of homocysteine in their plasma[7,8]. Although the causes are still under study, higher risk of fracture is strongly associated with increased levels of serum homocysteine . At the biochemistry level, it is basically a metabolite which is formed in the methionine metabolism. Cardiovascular, neuronal and pathologies linked to eyes are already proven to be associated with elevated serum homocysteine

levels. Folate and Vitamin B12 play vital role in the methionine metabolism and so the homocysteine[9]. They are basically the co-factors and external consumption of the above may decrease the levels of homocysteine in the blood [10, 11, 12]. Our target is to analyse the population with decreased Bone Mineral Density (BMD) and elevated serum homocysteine levels which may bring us to the conclusion that homocysteine is also one of the risk factors for osteoporosis.

OBJECTIVES

1. To correlate bone mineral density with serum homocysteine levels.

REVIEW OF LITERATURE

Osteoporosis is amongst the most familiar diseases in the older, and now is found to be associated with increased levels of homocysteine in the blood [13–15]. Fracture is one of the primary issues in patients with osteoporosis which prompts considerable harm, handicap and need for attention which is proved by the figures where every year around 2.5 million people suffer from osteoporotic fracture each year in the USA [16].

Homocysteine is an intermediate metabolite in metabolism of methionine and is situated at crossing point of two different metabolic paths, first is the re-methylation to methionine and second is the trans-sulphuration to cystathionine as depicted in Figure (1). In ordinary kidney work, its high serum level is for the most part identified with catalyst lack or B nutrient insufficiency (B6, folic acid and B12) [17]. Sexual orientation and the age both are the important determinants of homocysteine focuses in individuals. Blood plasma grouping of homocysteine increments with young fellows (matured 30 to 40 years) ordinarily have more Homocysteine levels than ladies (2 μmol/l approximately). Estrogen is associated with the separation between the males and females; in this manner, after the menopause the serum homocysteine level increments [18], while the age-subordinate rise of homocysteine is generally identified with functional lessening in kidney work [19,20].

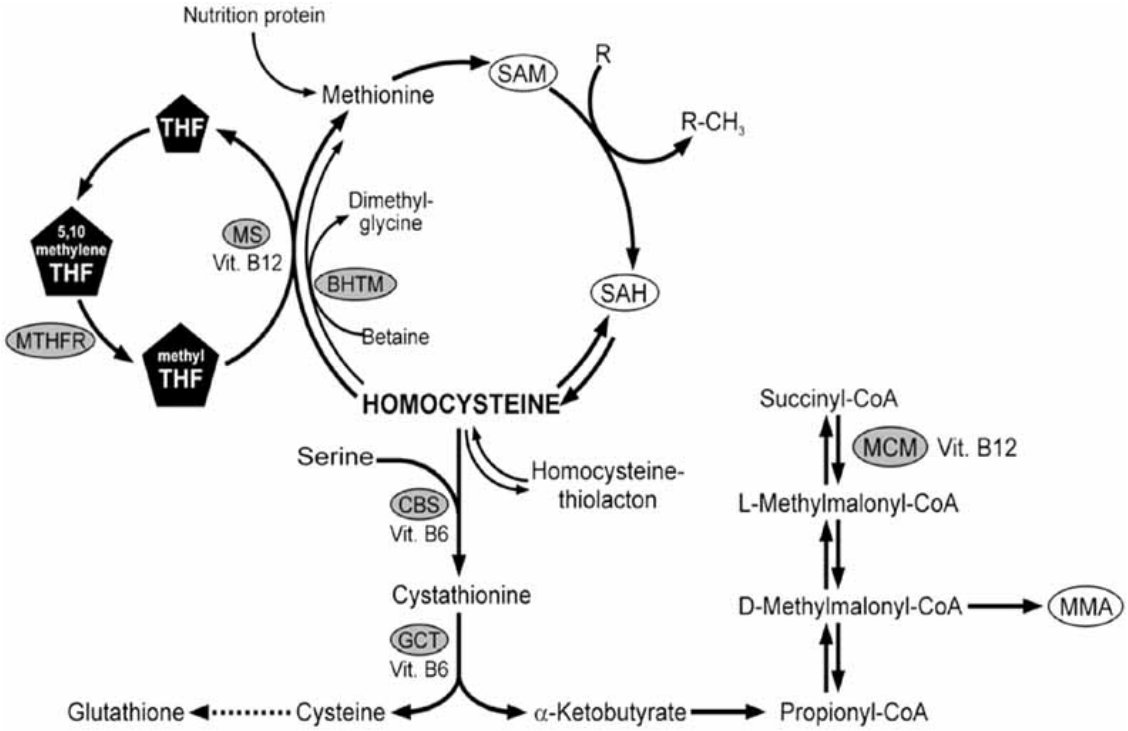


Figure 1 : Methionine metabolism.

MS- methionine synthase; SAM- S-adenosylmethionine; GCT-y-cystathionine; THF- tetrahydrofolate; MMA- methylmalonic acid; CBS-cystathionine-β-synthase; MTHFR- methylenetetrahydrofolate reductase; BHMT- betaine-homocysteine-methyltransferase; R-CH3-methylation product; MCM- L-methyl malonyl-CoA-mutase[5].

In the mid-1960s, homocysteine was accounted for as a pathological element. It is observed that a high flowing homocysteine is a free danger factor for a many illnesses, including Alzheimer and cardiovascular sicknesses [21]. Reasonable homocysteine levels convey around 10% of the absolute danger of cardiovascular infections [18,19,22]. What's more with homocystinuria is the pervasiveness of skeletal disfigurements [23–25]. It is additionally well-thought-out as a danger factor for neurodegenerative disorders, osteoporotic fractures and pregnancy intricacies. Truth

be told, raised plasma homocysteine focus builds the danger of hip crack, causing handicap [26], high clinical expenses [27] and demise [28].

homocysteine was first perceived as an answerable factor for mutations in homocystinuria patients in 1957[29]. These patients presented haphazard bone development, smoothed vertebral bodies, skeletal deformations and a low bone mass [30].

The relationship of serum homocysteine and folate levels on bone mineral thickness is examined in past examinations [13,14,31,39,40]. In vitro studies demonstrated the plausible impedance among homocysteine and its arrangement of collagen cross-joins, counteraction of fibrils in solubilization, restraint of enzyme lysyl oxidase and deferral in combination of more intricate cross-joints in collagen [32–34]. Be that as it may, regardless of whether homocysteine is the causative part or osteoporosis is brought about by different components of homocysteine metabolism has not been completely assessed at this point. B12 and the folic acid are significant parts of homocysteine digestion. Folate and its metabolites vary in the few body compartments like plasma as well as red platelets (RBCs). RBCs go about as a folate repository and keep up with folate homeostasis. In contrast to folic acid in plasma, RBC folate isn't influenced by exogenic factors, for example, medications and diet. Hence, there is likelihood that RBC folate as a drawn-out marker of the body predicts bone mineral density. Considering above, it is important to decide the specific impacts of homocysteine on decrepit conditions like osteoporosis. There is persuading proof in regards to the relationship of hyper-homocysteinemia with osteoporosis [35].

The connection among hyper-homocysteinemia and bone infections had not been perceived for quite a long time, until two imminent populaces not really settled a

possible connection between modestly raised serum homocysteine and the recurrence of osteoporotic breaks in the old populace [13,36].

van Meurs and his colleagues observed in Amsterdam and Rotterdam 2404 patients of age 55 or more for 11,253 man-years and noticed a relationship between homocysteine level and risk of break that was autonomous of BMD and other potential danger reasons for fracture [13].

McLean and his colleagues noticed in subgroup of the Framingham study population to have similar outcome [14]. The male fellows in that review with a normal mean age of 70 years with a homocysteine level in the third quartile had a risk of fracture which was 2.07-times more than men in the main quartile area. The break hazard for men in the fourth quartile was about 3.84-times more than for male fellows in the main quartile group. But this kind of relation was less clear in female group.

Be that as it may, Périer and his colleagues gotten various outcomes who were followed tentatively during a mean development of 10 years in 671 post-menopausal ladies, and inferred that homocysteine is not certainly an independent risk factor for osteoporotic cracks in sound postmenopausal ladies with an expansive age group [37].

Instruments of the connection among hyper-homocysteinemia and risk of fracture are obscure [38]. A few examinations broke down homocysteine corresponding to BMD, yet they showed no or just a feeble relationship between these two factors [39–41].

Truth be told, the feeble relationship amongst homocysteine and BMD isn't startling, since BMD is just a basic estimation of bone resorption throughout a more extended timeframe. They have estimated biochemical bone markers that show a continuous detecting of bone metabolism [39,42].

Dhonukshe-Rutten and his colleagues proved an expanded degree of osteon arrangement and also the markers of resorption in patients having hyper-

homocysteinemia[42]. Herrmann and his colleagues researched pre as well as post-menopausal ladies and found that homocysteine fixation is associated emphatically with urinary deoxypyridinoline crosslinks a bone resorption marker while not with the serum osteocalcin, a bone-development marker. They proposed that metabolism of bone goes in hand with the homocysteine metabolism [39]. Furthermore, osteoclast action was animated in the human osteoclasts (refined) with expanding portions of homocysteine which is in concurrence with speculation of expanded bone resorption within the sight of hyper-homocystenemia. Existing outcomes suggest that hyper-homocysteinemia can influence osteoclast action, however this information is not satisfactory to reason that osteoclast is the chief objective of homocysteine in human bone.

Then again, Gerdhem and his colleagues directed the review in 996 ladies from the Osteoporosis Perspective Risk Assessment study and recommended homocysteine as a danger reason. They noticed the connection between low BMD and high levels of bone-marker at benchmark. During an average 7-year follow-up, high homocysteine focus was related with mortality, yet no conspicuous connection to danger of fracture was noticed [43].

Kim and his group researched the impacts of homocysteine on stromal cells of bone marrow of humans. They saw that homocysteine prompts apoptosis in essential human stromal cells of human bone marrow through the responsive oxygen species-interceded NF-κB enactment and mitochondrial pathway in stromal cells of human bone marrow. homocysteine was noticed to add to the process of osteoporosis by decreasing bone arrangement. It was reasoned that in patients with hyper-homocysteinemia, cell reinforcements might play a part in forestalling bone resorption [44]. Koh and his colleagues played out the comparable report on osteoclasts

and proposed that homocysteine straightforwardly enacts development of osteoclasts by age of intracellular responsive oxygen species. In this manner, a cell reinforcement appears to constrict bone misfortune in hyper-homocysteinemia [45]. Nonetheless, Herrmann and his colleagues. exhibited that amassing of homocysteine by diminishing convergence of folate, nutrient B12 and B6 doesn't influence the movement of human osteoblasts [46]. Besides, the relationship among HYPER-homocysteine and diminished bone quality and upset bone digestion was affirmed in creature concentrates by Herrmann and his colleagues. What's more, Ozdem and his colleagues recommended that hyper-homocysteinemia is a causative factor for osteoporosis in rodents [47,48].

While in the old, hyper-homocysteinemia is essentially brought about by B complex insufficiency, it isn't notable whether these nutrients assume a huge part in bone well-being. Thinking about the systems, past investigations proposed a decrease in osteoblast movement in relationship with low nutrient B12 fixations [49,50].

Goerss and his colleagues seen that in patients with weakness (brought about by nutrient B12 insufficiency), the dangers of vertebral, proximal femur and lower arm fracture were 1.8, 1.9 and 2.8 times more than the controls, separately [51].

In one of the planned preliminary on 600 study population with osteoporosis and osteopenia, the significant job of B nutrients in bone wellbeing was considered. Sato and his colleagues treated the patients with 1500 μg B12 and 5 mg folate and placebo for two years and they noticed a roughly 75% lessening in the rate of fracture in the treatment bunch, which was similar with alendronate group [52].

Since we know of the various concentrations of folate in different compartments of body, Golbahar and his colleague's proposed folate in RBC as a preferred indicator of BMD over plasma folate. This might relate with pathogenesis of osteoporosis in the

post-menopausal women [35]. Roughly 1 year after the fact, Gjesdal and his colleagues. did one more review on 5338 older patients to look at the relationship between hip BMD and plasma levels of homocysteine, nutrient B12, folate and the polymorphism in methylenetetrahydrofolate reductase. They presumed that raised low folate levels and homocysteine were related with diminished BMD in ladies however not in men group [53].

In another new review, Green and his colleagues examined 276 more established subjects who were haphazardly relegated to get either every day supplement of B6, B12 and folate or false treatment for a long time. By estimating soluble phosphatase which is bone specific and bone-inferred collagen pieces at benchmark and the finish of study, they reasoned that supplementation with of B6, B12 and folate can bring down plasma homocysteine yet has no impact on turnover of bone [54].

Concerning the importance of folate, many studies concentrated on MTHFR polymorphism impacted by the C677T on bone. An expansion of fracture occurrence was distinguished with each T allele, particularly in patients with decreased levels of folate [55–57]. There are some disconnected outcomes in this regard. Li and his colleagues announced no relationship between the BMD of Chinese men or ladies and MTHFR. They reviewed it on, old ladies, postmenopausal ladies and old men. High nutrient B and folate consumption in the review populace added to the smaller number of patients and low pervasiveness in the TT genotype, ought to be considered [58].

Abrahamsen and his colleagues affirmed that in the most minimal quartile of folate, riboflavin, B6 and B12 consumption, BMD in TT genotype of MTHFR is just fundamentally decreased basically at the verge of menopause and B12 supplementation would just be expected to influence BMD in around 2 % of the

populace, like those with the low nutrient B12 group and TT genotype [59]. They additionally noticed critical skeletal his colleague's impact of this normal polymorphism in men at 25 years old years at lumbar spine [60].

Hong and his colleagues gotten comparative outcomes. To confirm the relationship of the BMD and fracture risk with MTHFR polymorphism, they included 1899 postmenopausal Chinese ladies. They showed that the MTHFR polymorphism is a free indicator of fracture, despite the fact that it just weakly affected BMD [61]. Other than advanced risk of fracture, low coursing levels of nutrient folate and B12 are additionally connected with low BMD which is in concurrence with the connection among homocysteine and BMD [62–65].

Baines and his colleagues concentrated on the connection between folate, nutrient B6, nutrient B12, MTHFR genotype and plasma homocysteine and BMD in 328 postmenopausal ladies. As per the gauge BMD, the subjects were doled out to three groups that is osteopenia, osteoporotic and the control. The osteoporotic patients manifested an essentially lower folic acid levels in the serum and a higher rate of fracture. Taking everything into account, they tracked down that low folate serum level is a significant danger factor for process of osteoporosis while the homocysteine level having a lesser significance. The two nutrients B6 and B12, by influencing homocysteine, may likewise affect the skeleton, albeit a more vulnerable one than folate [66].

TABLE 1 : Impact of Homocysteine on Bone: Studies on Human

Year	Study	Study Population	Results	Ref.
2004	van Meurs *and his colleagues*	2404 (55 years) elderly patients	1.4-fold increase in risk of fracture per SD rise in homocysteine	[13]
2004	Li *and his colleagues*	657 Chinese men and women	No link between *MTHFR* polymorphism and BMD	[58]
2004	McLean *and his colleagues*	1174 women and 825 men aged 59–91 years	Higher homocysteine had more risk of fracture in men especially	[14]
2005	Dhonukshe-Rutten *and his colleagues*	652 women and 615 men (age: 76 ± 6.6 SD years)	Association of High homocysteine and low B12 levels, high risk of fracture	[42]
2005	Abrahamsen *and his colleagues*	1700 post-menopausal women	B1, B6, B12 and folic acid + *MTHFR* TTgenotype association with BMD	[59]
2005	Dhonukshe-Rutten *and his colleagues*	73 (9–15 years) school going	Low BMD is associated with the impaired cobalamin status.	[62]
2005	Hermann *and his colleagues*	143 peri-menopausal females	Feeble but important relationship between bone resorption and homocysteine	[39]
2005	Golbahar *and his colleagues*	366 postmenopausal women	RBC containing folate deficiency is linked with decreased BMD	[35]
2006	Abrahamsen *and his colleagues*	780 (20–29 years) Danish men	Many skeletal changes at lumbar spine in men at 25 years with *MTHFR* polymorphism	[60]

2006	Gjesdal *and his colleagues*	(Hordaland study) women(71–75 years) and 5338 men (47–50 years)	In women, hyper-homocysteinemia and low folic acid levels were linked with low BMD.	[62]
2007	Gerdhem *and his colleagues*	996 women (75 years)	homocysteine being the bone resorptive marker	[43]
2007	Hong *and his colleagues*	1899 Chinese postmenopausal women	Polymorphism of MTHFR is a lone risk factor for fracture risk but have less effect on bone mineral density	[61]
2007	Baines *and his colleagues*	328 British postmenopausal women	Osteoporosis is more affected by Low folate than the homocysteine	[66]
2007	Green *and his colleagues*	276 well healthy subjects	Supplementation with vitamin B12, B6and folate have lowered plasma homocysteine but after 2 years no change was observed	[54]
2007	Périer *and his colleagues*	(OFELY study) 671 postmenopausal women	homocysteine is certainly not an autonomous risk factor for fracture	[37]

SD – standard deviation; ROS; reactive oxygen species; *MTHFR - Methylenetetrahydrofolate reductase* ; DPD – Deoxypyridinoline; *OC – Osteocalcin*

TABLE 2 : Homocysteine effects on bone: animal studies and cell cultures

Year	Study	Hypothesis	Results	Ref.
2006	Kim *and his colleagues*	homocysteine causes apoptosis ofosteoblasts	homocysteine causes apoptosis in boscs through ROS	[44]
2006	Koh *and his colleagues*	Effect ofhomocysteine on osteoclast formation	homocysteine straightforwardly initiates osteoclast development and activity	[45]
2007	Herrmann *and his colleagues*	hyper-homocysteinemia decreases activity of osteoblast	No effect of hyper-homocysteinemia onosteoblast activity	[46]
2007	Herrmann *and his colleagues*	hyper-homocysteinemia being the cause for osteoporotic fractures in rats	hyper-homocysteinemia decreases bone quality in rats	[47]
2007	Ozdem *and his colleagues.*	Bone metabolism is disturbed by hyper-homocysteinemia	Significant bone turnover in rats with hyper-homocysteinemia	[48]

ROS - Reactiveoxygen species, hBMSC - human bone marrow stromal cells

Adding to their studies [46,47] Herrmann and his colleagues in 2008 inferred that the review gives proof to a collection of homocysteine in bone tissue of hyper-homocysteinemic creatures that was associated with great loss of bone and a decrease of bone strength. This affirms our theory that hyper-homocysteinemia has direct negative consequences for bone. The current information further shows that most of homocysteine in bone is attached to extracellular collagen. Moreover, hyper-homocysteinemia appears to diminish the methylation limit in bone as an extra pathomechanism of possible significance. Future investigations will be needed to

additionally explain the pathomechanisms of hyper-homocysteinemia in bone as a typical and modifiable danger factor of osteoporosis [67].

Restricting the above literature [42,59,62,66] Rumbak and his colleagues in 2011 has shown that in their populace of sound Croatian matured 45–65 years females, homocysteine, folate or B12 levels can't be considered as indicators of BMD. Studies with bigger samples are expected to explain the relationship of homocysteine, folate, B12 with regards to loss of bone or even case control trials studies to test whether supplementation with folate and additionally nutrient B12 could affect [68].

Again, going against to their literature [37,66], Bahtiri and his colleagues in their review in 2015, shows that homocysteine status, however not B12 status, is related with BMD in this associate of postmenopausal ladies. They henceforth affirmed that high homocysteine levels are a free danger factor for osteoporosis. BMD assessment in ladies at post menopause with high homocysteine levels might be useful in exhorting prudent measures [69].

In 2016, Zhu and his colleagues expressed that serum homocysteine levels with Osteoporotic fractures (OPFs) patients were fundamentally more as compare to patients with no history of fracture. Serum homocysteine level isn't connected with bone mineral density in patients, yet is corresponded in bone digestion with osteoclast bone resorption markers. Serum homocysteine level can be as a significant danger factor for OPFs in the older populace. Lessening serum homocysteine level can work on bone quality and diminish the danger of dropping in older patients optional to skeletal muscle or bone along these lines decreasing the danger of OPFs in the old. To foresee the event of OPFs is the course for further research [70].

Ravichandran S in 2016 accompanied the end that individuals with high serum homocysteine had a diminished BMD, in this manner building up a relationship

among homocysteine and the danger of creating osteoporosis. While adding to the query [66,54,37] he inferred that Vitamin B12 and folate assume a significant part in homocysteine digestion. B12 and folate supplementation has been displayed to standardize plasma homocysteine levels. This will turn around the issue of impeded bone wellbeing and osteoporosis which will help in preventing OPFs [71].

In 2018, Gopinath P and his colleagues showed that homocysteine status is related with BMD in osteoporotic postmenopausal ladies. BMD assessment in postmenopausal ladies with high homocysteine levels might have prognostic and remedial possibilities while which should be investigated through additional Prospective studies [72].

One more feature in 2018 by Saoji R and his colleagues evaluated the relationship between lipid boundaries and BMD in a youthful ancestral populace which have not been sufficiently addressed in past investigations. They traditionally recognized for cardiovascular wellbeing, high HDL and low homocysteine as positive clinical relates related with ordinary BMD at both the spine and femur. Curiously, proatherogenic high TG levels associated emphatically with BMD at both the destinations. Rather than past examinations, we didn't notice any effect of way of life factors (tobacco and liquor utilization) on this affiliation. This could be a direct result of the youthful populace in our review, as the impacts of these way of life factors might get intensified sometime down the road. All things considered, the result of this review states that the two substances BMD and lipid boundaries (HDL and TG) with homocysteine might be seen all the while as a preventive methodology for signs of sicknesses related with low BMD and dyslipidemia [73].

In 2019, Tinelli C and his colleagues clarified at natural chemistry level that as we probably are aware Homocysteine is a key substance engaged with the digestion of

methionine, which assumes an essential part in the normal cell's life cycle. homocysteine fixation increment is by all accounts caused predominantly by the generally diffused polymorphisms of a few proteins. Delayed openness to this disorder can prompt the beginning of cardiovascular illness and can prompt the advancement of stroke, atherosclerosis, incendiary disorders like osteoporosis and stiffness, neuronal including Alzheimer's and Parkinson's disease. Here we dissected the writing of a few neurotic conditions involved in the pathways of hyper-homocysteinemia at the atomic level. Strangely, a few perceptions demonstrate that the adjusted supposition of right dosages of nutrients, for example, folate, B6, B12 might control hyper-homocysteinemia related conditions [74].

De Martinis M and his colleagues contemplated in 2020 and recommended a huge relationship among homocysteine and postmenopausal osteoporosis. Not with-standing the numerous endeavors to viably analyze and forestall osteoporosis event, the outcomes are not completely acceptable. An unevenness in homocysteine digestion might add to an insanity of bone rebuilding, preferring the start of osteoporosis. The standard of homocysteine overproduction and the adjustment of the provocative substratum that describes menopause might address extra restorative methodologies for osteoporosis counteraction and control [75].

The size was the significant strength of this review. Zhongxin Zhu and his colleagues explored plasma total homocysteine and lumbar BMD of 10748 examples of the multiracial populace. Consequently, subgroup examinations could be performed because of the enormous example size. They found the relationship between plasma homocysteine level inside ordinary reach and lumbar BMD contrasted by age and sexual orientation. Their discoveries give comparable experiences to propel the exploration of the connection among homocysteine and bone health [76].

Fortifying to research [42], Sandeep MMR and his colleagues in 2020 additionally focused those individuals with low Bone Mineral Density (BMD) and detected to have high levels of homocysteine in the blood. Hence it builds up a relationship among homocysteine and the danger of creating osteoporosis. Nutrient B12 and folate assume a significant part in homocysteine digestion. Supplementation with B12 as well as folate has been displayed to standardize serum homocysteine levels. This might switch the issue of disabled osteoporosis and help in forestalling OPFs [77].

MATERIALS AND METHOD

The above study was conducted in Department of Orthopaedics, JNMC KAHER, KLE's Hospital, Belagavi.

Study Design :

Cross sectional study- One year.

Data Source :

Patients between the age of 40 to 70 years fulfilling the inclusion criteria who had come to OPD or admitted to KLE's Hospital, Belagavi.

Sampling Size :

In all Eighty patients who aged between forty to seventy years were nominated who fulfil the inclusion criteria and were willing to participate in this study.

Sampling Method :

Equation = 4pq / d2

p - Osteoporosis prevalence in percentage

(Study was done in Bangalore (2017) who matched the demography of our study) .

It was approximately 29% and q = 100 - p %,

d = absolute error of 10%.

***Inclusion Criteria* =**

I. Patients between 40 to 70 years of age.
II. Patients who are willing to participate in this study

***Exclusion Criteria* =**

1. Patients who are on following medications which can affect the calcium metabolism :
    I. Anti-epileptics - Thyroxine
    II. Long term steroids
    III. Heparin and its congeners

IV. Thyroid hormone supplements like Thyroxine
V. Oestrogen
VI. Thiazide diuretics

2. Patients with chronic diseases as follows :

I. Chronic kidney diseases
II. Chronic liver disease
III. Rheumatoid Arthritis
IV. Chronic skin disease
V. Chronic bed ridden patients
VI. Malignancy

Method :

The patients fulfilling the inclusion criteria and willing to participate were selected and enrolled in after getting clearance from Jawaharlal Nehru Medical College Ethical and Research Committee. The written consented (Annexure- I) patients were registered for our study and underwent required investigations. Added, personal information of patient and required related history was assessed by a questionnaire (Annexure – II).

Investigations :

A. Bone Mineral Density was assessed using Dual Energy Xray Absorptiometry Scan: Lunar model, 2008 GE Wipro.

Procedure of DEXA Scan :

DEXA Scan uses a computer software and a Xray machine to check for the bone mineral density. It gives precise as well as reproducible calculation of bone mineral density.

Pre-requisites for Scan :

1) Written and Informed consent
2) Patients fulfilling the inclusion as well as criteria exclusion
3) Patient information and data by the questionnaire

Instructions before scan :

1. Clothes and accessories should be removed containing any metal or wear a gown for better results.
2. Patient shouldn't move during the process.

Procedure :

The process is free of pain and takes only about ten minutes. The scanning apparatus expose body to a tiny dose of X-ray. Radiographer handles the whole machinery.

Scan is directed over Lumbar Spine. Patient is requested to bend the legs which helps in straightening of spine. Scanning is done with the help of Xray tube which is mobile and passes over the lumbar spine emitting the x-ray beams. During this process, a fraction of Xray radiation is absorbed by lumbar spine . This amount of absorption will reflect the bone mineral density.

The system has a receiver which calculates the x-ray radiation passing through the lumbar spine and directs the whole data to a connected computer. A written printed copy of report is obtained asserting the T score, Z score and BMD.

To check the Homocysteine levels in blood, 5 ml of venous blood is drawn from the antecubital vein and is then collected in the EDTA tube and send to biochemistry laboratory. Homocysteine levels were measured by Enzyme based immunoassay.

A homocysteine test estimates the measure of homocysteine in your blood. Homocysteine is a kind of amino acid, a compound your body uses to make proteins. Regularly, nutrient B12, B6, and folic acid separate homocysteine and change it into different substances your body needs. There ought to be very little homocysteine left in the circulation system which goes from 5 to 15 micromoles(mcmol)/L . The outcomes were gathered and broke down to check whether there is any association between osteoporosis and serum homocysteine.

Interpretation :

- T score will be interpretated as follows :

WHO Criteria for 'T' score -

Normal : 'T' score at or above -1 SD

Osteopenia : 'T' score between -1 to -2.5 SD

Osteoporosis : 'T' score at and above -2.5 SD

- Serum Homocysteine levels will be interpretated as follows :

Normal : 5 – 15 mcmol/L (micromoles per litre)

Elevated : > 15 mcmol/L (micromoles per litre)

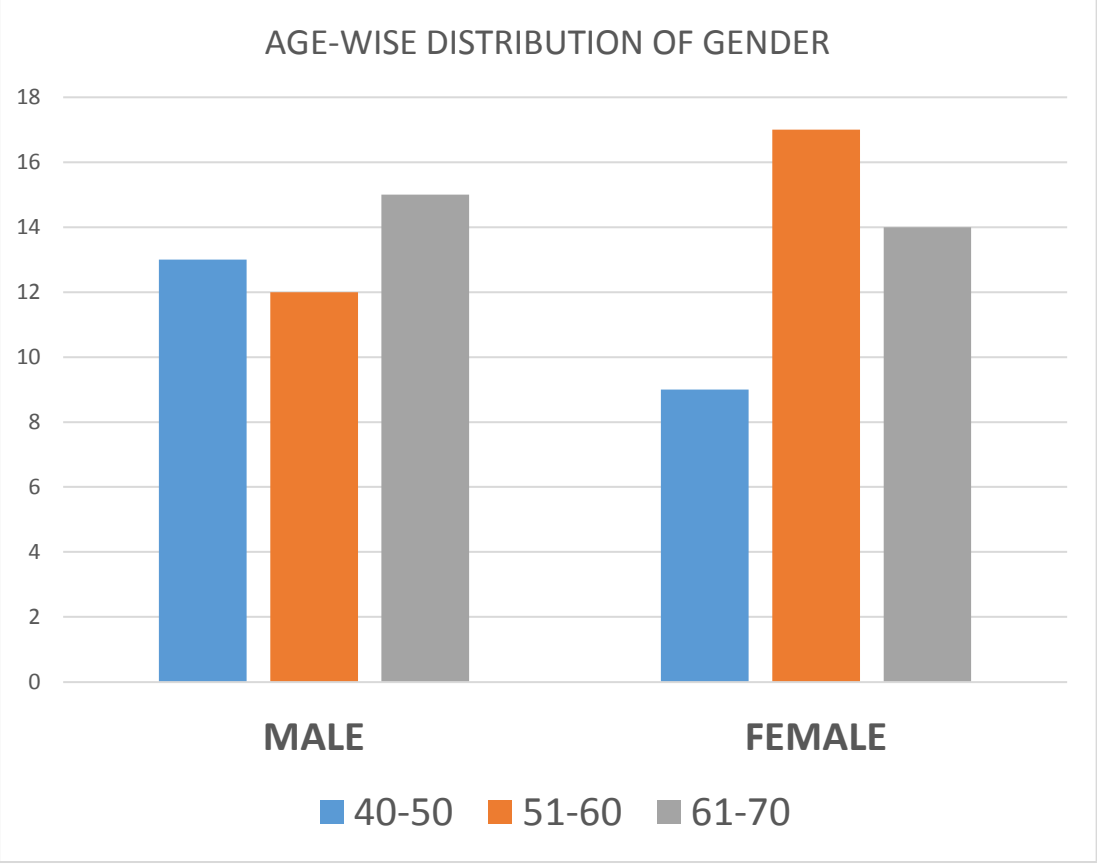
RESULTS

In this study period of 1 year , 80 patients who fell into our inclusion criteria were included in our study. Below are the observations -

There are total 40 males and 40 females. 13 males belong to the age group of 40-50 years, 12 males are between 51-60 years and 15 of them belong to 61-70 years. There are 40 females included in the study as well. 9 of them are from 40-50 years of age, 17 from 51-60 years while 14 belong to the age group of 61-70 years.

Table 3: Age distribution

Age group (Years)	Male	Female
40 - 50	13	9
51 - 60	12	17
61 - 70	15	14

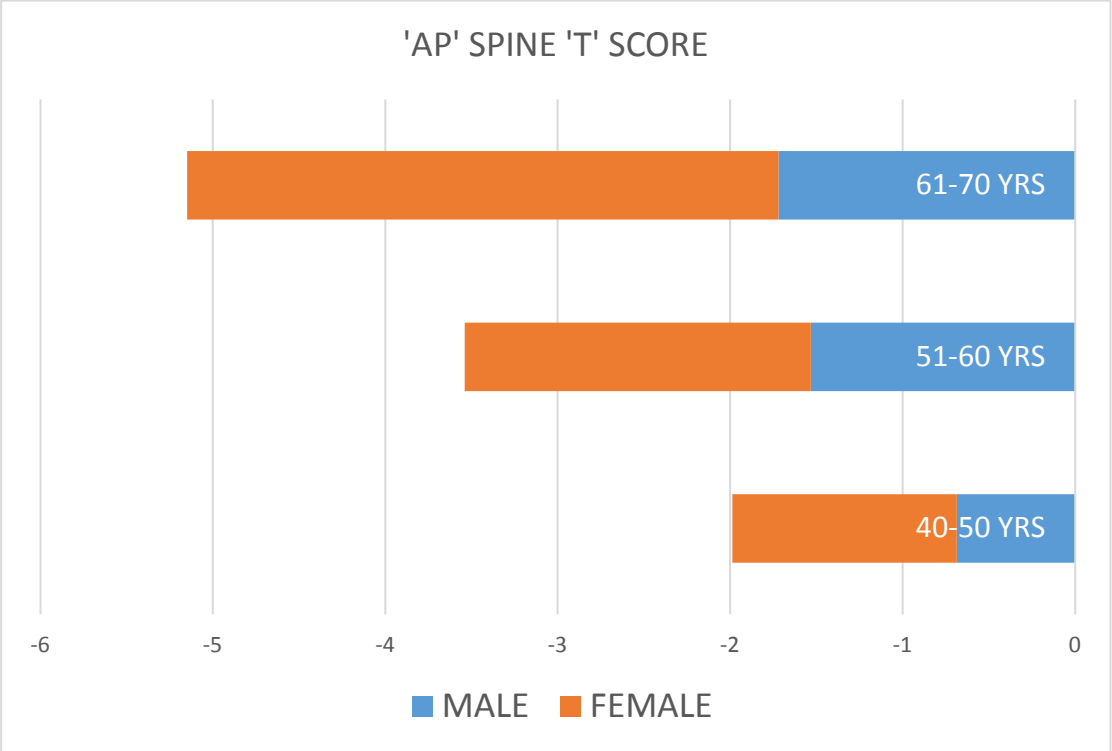


Graph 1- Age-wise Distribution of Gender

The average BMD was -0.68 and -1.3 in males and females respectively in 41-50 years age group. It was -1.533 and -2.005 in males and females respectively in 51-60 years age group and -1.720 and -3.428 in males and females respectively in 61-70 years age group.

Table 4 : 'AP' SPINE 'T' SCORE

Age group(Years)	**Males**	**Females**
40-50	-0.686 ± 0.59	-1.300 ± 1.17
51-60	-1.533 ± 1.09	-2.005 ± 1.40
61-70	-1.720 ± 0.97	-3.428 ± 0.95



GRAPH 2: Average 'AP' SPINE 'T' SCORE among males and females of different age groups

In the age group of 40-50 years, only 4 out of 13 males were osteopenia while remaining all had normal BMD while 2 out of 13 females were osteopenia and another 2 were osteoporotic. In the age group of 51-60 years, 2 osteoporotic and 6 osteopenia out of 12 males were observed while in females in same age group 8 osteopenia and 5 osteoporotic out of 13 were observed. In the age group of 61-70 years 9 osteopenia and 3 osteoporotic were observed out of 15 males while 13 out of 14 females were osteoporotic in identical age group.

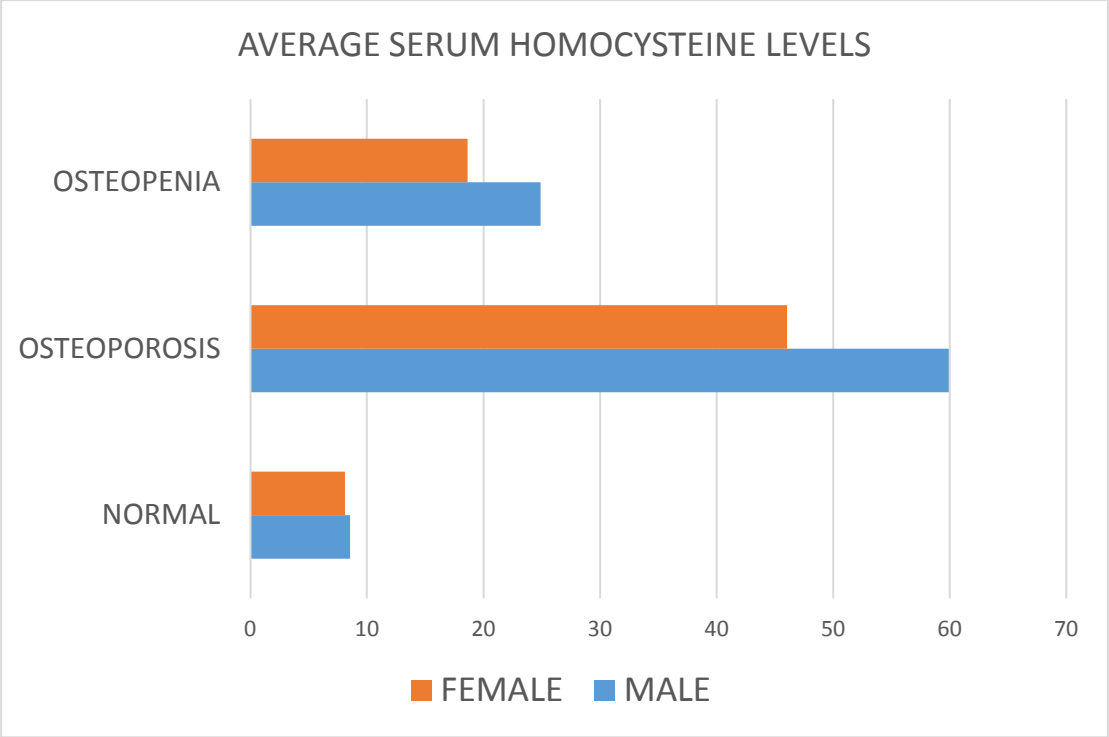
TABLE 5: Sex and Age-related BMD distribution

Bone Marrow density	**Males(n)**			**Females(n)**		
	40-50	51-60	61-70	40-50	51-60	61-70
Normal	9	4	3	5	4	0
Osteopenia	4	6	9	2	8	1
Osteoporosis	0	2	3	2	5	13

Average plasma Homocysteine was 8.558 mmol/L and 8.121 mmol/L in males and females respectively in normal BMD patients. It was 24.894 mmol/L and 18.63 mmol/L in males and females respectively in Osteopenia group while it was 59.92 mmol/L and 46.061 mmol/L in males and females respectively in osteoporotic group.

TABLE 6 : Average Serum Homocysteine

Bone Marrow density	Males(mmol/L)	Females(mmol/L)
Normal	8.558 ± 3.76	8.121 ± 3.26
Osteopenia	24.894 ± 11.80	18.630 ± 6.57
Osteoporosis	59.920 ± 4.02	46.061 ± 23.25



GRAPH 3: Average Serum Homocysteine levels of males and females with different Bone Mineral Density

CORRELATION BETWEEN 'AP' SPINE 'T' SCORE and SERUM HOMOCYSTEINE

There is a negative correlation between 'AP' spine 'T' score and serum homocysteine (-0.820). It means that both the variables move in the opposite direction. An increase in serum homocysteine levels is associated with decrease in Bone mineral density. The correlation between them is statistically significant with $p<0.05$.

Correlations

			'AP' SPINE 'T' SCORE	SERUM HOMOCYSTEINE
Spearman's rho	'AP' SPINE 'T' SCORE	Correlation Coefficient	1.000	-.820**
		Sig. (2-tailed)	.	.000
		N	80	80
	SR. HOMOCYSTEINE	Correlation Coefficient	-.820**	1.000
		Sig. (2-tailed)	.000	.
		N	80	80

****. Correlation is significant at the 0.01 level (2-tailed).**

TABLE 7 : SPEARMAN'S CORRELATION

SPEARMAN'S CORRELATION	**Correlation coefficient**	**Level of Significance (p-value)**
'AP' SPINE 'T' SCORE	-0.820	0.000
SERUM HOMOCYSTEINE		

***P<0.05= statistically significant**

LINEAR REGRESSION BETWEEN 'AP' SPINE 'T' SCORE and SERUM HOMOCYSTEINE

Linear regression is denoted by the formula y=mx+c, where y is the dependent variable (serum homocysteine), m is the slope which is the unstandardized coefficient of -12.059 (negative slope) and c is the constant of 4.211. Linear Regression shows that, rise in the serum homocysteine levels by 12.059 mmol/L decreases the bone mineral density by one standard deviation 'AP' spine 'T' score. The negative unstandardized coefficient is statistically significant as the p<0.05.

Coefficients

Model		Unstandardized Coefficients		Standardized Coefficients		
		B	Std. Error	Beta	t	Sig.
1	(Constant)	4.211	2.642		1.594	.115
	'AP' SPINE 'T' SCORE	-12.059	1.164	-.761	-10.359	.000

a. Dependent Variable: serum homocysteine

TABLE 8 : LINEAR REGRESSION

LINEAR REGRESSION	**Unstandardized coefficient**	**Level of Significance (P- VALUE)**
'AP' SPINE 'T' SCORE	-12.059	0.000
SERUM HOMOCYSTEINE		

***P<0.05= statistically significant**

DISCUSSION

Osteoporosis is not limited to postmenopausal women which was earlier thought to be a part of aging[2]. Osteoporosis is similar to Diabetes Mellitus in a way that it silently progresses until the patient presents with the osteoporotic fracture. It is becoming the major concern in developing countries like India where it goes undiagnosed in majority of population[1].

Osteoporotic fractures have caused huge financial loss by increasing the morbidity as well as the mortality. Almost 7 % of the women are dependent for their basic daily activities due to the spine, hip and distal forearm osteoporotic fractures. Most influential is the hip fracture which has decreased the expected survival by 12–20%[3, 4, 5]. Moreover, in terms of financial burden, cost also changes depending upon the place whether metro city or a town or a village and type of hospital as well. Hip surgery cost around 1.5 to 2.5 lakhs in private setups while it is around 50 thousand in government hospitals[6].

Increased levels of serum homocysteine have been found to be associated with the early start of osteoporosis[7,8]. It was surprising to acknowledge that 30 to 50 % of the population which is above 60 years have increased levels of homocysteine in their plasma[7,8]. in the mid-1960s, homocysteine was accounted for as a pathological element. It is observed that a high flowing homocysteine is a free danger factor for a many illnesses, including Alzheimer and cardiovascular sicknesses [21]. What's more with homocystinuria is the pervasiveness of skeletal disfigurements [23–25]. It is additionally well-thought-out as a danger factor for neurodegenerative disorders, osteoporotic fractures and also associated with intricacies in pregnancy. Truth be told,

raised plasma homocysteine focus builds the danger of hip crack, causing handicap [26], high clinical expenses [27] and demise [28].

In 2012 , Vacek TP and his colleagues presumed that Homocysteine influences biology of bone. He proposed homocysteine as a significant part in bone remodelling[79]. Adding evidence to above , Behra J concluded that Homocysteine directly activates osteoclast formation via increase in oxidative process like mitochondrial matrix metalloproteases activation leading to degradation in bone matrix and alteration in the biological as well as mechanical properties of the skeleton. So, osteoclasts mediated bone resorption may lead to osteoporosis in people with mild-moderate hyper-homocysteinemia[81].

Finally in 2019, Tinelli C and his colleagues clarified at natural chemistry level that hyper-homocysteinemia is by all accounts caused predominantly by the generally diffused polymorphisms of a few proteins. Delayed awareness prompts the beginning of cardiovascular illness and can prompt the advancement of atherosclerosis, stroke, incendiary disorders for example osteoporosis and stiffness, neuronal pathologies including Alzheimer's and Parkinson's sicknesses [74].

Zhongxin Zhu and his colleagues came with huge sample size in 2019 who explored plasma homocysteine and lumbar BMD of 10748 examples of the multiracial populace. Their discoveries give comparable experiences to propel the exploration of the connection among homocysteine and bone health [76]. In 2016, Ravichandran S and his colleagues presumed that individuals with high flowing degrees of homocysteine had diminished bone density accordingly building up a reverse relationship between the serum homocysteine and the osteoporosis[71]. Fortifying to

research [42], Sandeep MMR and his colleagues in 2020 additionally focused those individuals with higher coursing level of homocysteine had a diminished Bone Mineral Density, hence building up a relationship among homocysteine and the danger of creating osteoporosis [77].

Likewise, in our review, we tracked down a converse relationship between plasma homocysteine levels and BMD. Average plasma homocysteine was less than 10 in normal BMD patients. It was 24.894 mmol/L and 18.63 mmol/L in males and females respectively in Osteopenia group while it was 59.92 mmol/L and 46.061 mmol/L in males and females respectively in osteoporotic group.

In 2018, Gopinath P and his colleagues showed that homocysteine status is related with BMD in osteoporotic postmenopausal women. BMD assessment in postmenopausal ladies with high homocysteine levels might have prognostic and remedial possibilities while which should be investigated through additional Prospective studies[36,66,69,72]. De Martinis M and his colleagues contemplated in 2020 and recommended a huge relationship among homocysteine and postmenopausal osteoporosis. Not with-standing the numerous endeavors to viably analyze and forestall osteoporosis event, the outcomes are not completely acceptable. An unevenness in homocysteine digestion might add to an insanity of bone rebuilding. The guideline of homocysteine overproduction and the adjustment in provocative substrate that describes menopause might address extra restorative methodologies for osteoporosis counteraction and control [75]. Bone resorption markers, inflammation, prevalence of C677T polymorphism and homocysteine were higher, whereas bone formation markers, vitamin B12, folate and Vitamin D were on a lower side with women having decreased BMD in comparison with the normal BMD. Another study in relation to osteoporosis in postmenopausal women suggest a strong link between

inflammation, homocysteine and BMD. The control and regulation of homocysteine and inflammation might represent extra approaches for the prevention of postmenopausal osteoporosis [75].

In 2014, ebwsunan and his colleagues expressed that there is critical increase in serum homocysteine with comparing decline in folate, B12 and B6 and are connected with decline in bone mineral thickness. So, decline in the above minerals could be a significant danger factor for osteoporotic fracture. Supplementation with the B complex might be helpful for the patients[80]. This might switch the issue of impeded wellbeing of bone and help in forestalling osteoporotic fractures[71,77].

Upcoming point of interest is the causality of osteoporosis in young due to the changing lifestyle surrounded with many risk factors. Saoji R and his colleagues evaluated the relationship between lipid boundaries and BMD in a youthful ancestral populace which have not been sufficiently addressed in past investigations. Surprisingly, proatherogenic high TG levels were associated with low BMD as well. All things considered, the result of this review states that the two substances BMD and lipid boundaries (HDL and TG) with homocysteine might be seen all the while as a preventive methodology for signs of sicknesses related with low BMD and dyslipidemia. Studies in the past, didn't notice any effect of life style (tobacco and liquor utilization) on this affiliation. This could be a direct result of the youthful populace in our review, as the impacts of this lifestyle might get intensified sometime down the road. [73].

CONCLUSION

Avoidance of osteoporosis by distinguishing the danger factors is a significant test in the field of medicine. Bone turnover is influenced by homocysteine. Raised homocysteine level in blood is a potential danger factor for the osteoporosis to develop. In our study, the burden of Osteoporosis was 31.25 % with females in majority contributing 50 % of the participants. The average age for both men and women were 62 years ranging from 40 to 70 years .

In this cross-sectional study, 80 individuals were evaluated to correlate bone mineral density with serum homocysteine levels. From our study, there is a negative Spearman's correlation between 'AP' spine 'T' score and serum homocysteine (-0.820). An increase in serum homocysteine levels cause a decrease in bone mineral density. The correlation between them is statistically significant with $p<0.05$. Linear Regression shows that, rise in the serum homocysteine levels by 12.059 mmol/L decreases the bone mineral density by one standard deviation 'AP' spine 'T' score. The negative unstandardized coefficient is statistically significant as the $p<0.05$. With consideration of Spearman's correlation and Linear Regression raised homocysteine levels in blood may be stated as a potential risk factor for process of Osteoporosis.

Nutrient B12 and folate play a significant job in metabolism of homocysteine. Supplementation with B12 and folate vitamins has been displayed to standardize serum homocysteine levels. This might turn around the issue of impeded bone wellbeing and help in forestalling osteoporotic fractures.

Osteoporosis is a significant medical issue which has pulverizing and devastating results since it is associated with osteoporotic fractures.

SUMMARY

- The study was done to correlate the serum homocysteine levels with the bone mineral density.
- Study Objective:
  - To correlate bone mineral density with serum homocysteine levels.
- Using the set of questions, personal data, demographic information was gathered and those who fulfilled the inclusion-exclusion criteria were selected for the study.
- Patients were investigated with DEXA Scan and were assessed using 'T' scores. Then the blood sample was withdrawn to test the serum homocysteine levels.
- Statistical analysis was done using SPSS software to assess the results.
- There is a negative Spearman's correlation between 'AP' spine 'T' score and serum homocysteine (-0.820). An increase in serum homocysteine levels cause a decrease in bone mineral density. The correlation between them is statistically significant with $p<0.05$. Regression shows that, rise in the serum homocysteine levels by 12.059 mmol/L decreases the bone mineral density by one standard deviation 'AP' spine 'T' score. The negative unstandardized coefficient is statistically significant as the $p<0.05$. With consideration of Spearman's correlation and Linear Regression, raised Homocysteine levels in blood can be stated as a potential risk factor for skeletal Osteoporosis.
- Supplementation with B12 and folate vitamins could turn around the issue of impeded bone wellbeing, osteoporosis and help in forestalling osteoporotic fractures.

LIMITATIONS OF THE STUDY

- Single investigator conducted the study.
- Study is single centric with a smaller sample size i.e 80. Hence, we propose multicentric studies and samples with large sizes to evidence parallel hypothesis.

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INFORMED CONSENT

"CORRELATION BETWEEN SERUM HOMOCYSTEINE LEVELS AND THE RISK OF OSTEOPOROSIS – A ONE YEAR HOSPITAL BASED CROSS SECTIONAL STUDY."

PRINCIPAL INVESTIGATOR:

INTRODUCTION AND PURPOSE: The present study is conducted among patients who are presenting to orthopaedics OPD/IPD of KLE Dr. PRABHAKAR KORE HOSPITAL AND MRC, BELAGAVI aged between 40 years to 70 years to assess the **CORRELATION BETWEEN SERUM HOMOCYSTEINE LEVELS AND THE RISK OF OSTEOPOROSIS**. You are requested to participate in the study and your participation is completely voluntary.

PROCEDURE: If you agree to participate in this study, the relevant data will be collected as per the proforma and the final diagnosis will be confirmed. After getting inducted in the study, you will be evaluated, complete detailed history will be taken and thereafter blood sample will be withdrawn to check serum homocysteine levels, followed by DEXA scan will be done on OPD or IPD basis. The procedure is done only once.

BENEFITS:

1) You will not be eligible for any kind of monetary benefits or free services by virtue of participation in the study.
2) As an ailment in early diagnosis and treatment initiation in osteoporosis.

RISKS:

No risks associated with the study.

WITHDRAWING / REMOVAL FROM STUDY:

You can withdraw from the study anytime you want to.

PRIVACY AND CONFIDENTIALITY:

All information about the subject during the course of the study will be kept confidential to the extent permitted by law.

COSTS:

HOMOCYSTEINE TEST – RS 900

DEXA SCAN – RS 1200

AUTHORISATION TO PUBLISH THE RESULTS:

The researcher may use the information gathered from this study for presentation in scientific meetings. However, your identity will not be revealed.

QUERIES:

If you have any queries regarding study, you can contact without any hesitation and the guide. If you have any questions about rights of a research participant, you can contact: Professor of Dept. of Pediatrics and Chairman Ethical Committee on Human subjects, J. N MEDICAL COLLEGE, BELAGAVI.

CONSENT SUMMARY:

I have been explained all the contents of this consent form in my vernacular language and having understood and clarified all my queries about the study to best of my knowledge, i hereby give voluntary consent for participation in the study. I do sign the informed consent form in front of an eyewitness whom i recognize.

NAME AND SIGNATURE / LEFT THUMB IMPRESSION OF THE PARTICIPANT:

NAME AND SIGNATURE OF THE INTERVIEWER:

NAME AND SIGNATURE / LEFT THUMB IMPRESSION OF EYEWITNESS:

SIGNATURE OF THE GUIDE

DATE:

ANNEXURE II. ETHICAL CLEARANCE.

K.L.E. ACADEMY OF HIGHER EDUCATION AND RESEARCH
(Deemed – to- be- University)
Accredited 'A' Grade by NAAC (2nd Cycle) Placed in Category 'A' by MHRD (GoI)
JAWAHARLAL NEHRU MEDICAL COLLEGE,
NEHRU NAGAR, BELAGAVI-590010 (KARNATAKA-INDIA)
Website: http//www.jnmc.edu
E-Mail : dome@jnmc.edu
Phone: (+ 91-(0)831 Office : 2472550
Principal: 2471701
Fax No. +91 (0)831 – 2470759

Ref: MDC/DOME/ 244 **Date: 24/12/2019**

To,
BL0119005
PG student in Orthopaedics,
J.N.Medical College,
BELAGAVI.

Sub: Institutional Ethical Clearance for the study.

With reference to the above, we wish to inform you that your proposed research project titled **"CORRELATION OF SERUM HOMOCYSTEINE LEVELS AND THE RISK OF OSTEOPOROSIS- ONE YEAR HOSPITAL BASED CROSS SECTIONAL STUDY ",** is ethical and justifiable. The proposed research project has been cleared by the JNMC Institutional Ethics Committee on Human Subjects Research.

(Dr. Anita Dalal)
Member Secretary
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

(Dr. Roopa M Bellad)
Chairman,
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

PROFORMA

"CORRELATION BETWEEN SERUM HOMOCYSTIENE LEVELS AND THE RISK OF OSTEOPOROSIS- ONE YEAR HOSPITAL BASED CROSS SECTIONAL STUDY."

Patient id -

Name: **Age:**

Address:

Occupation:

Weight: **Height:** **:** **kg/m^2**

Chief complaints:

1)

2)

1) On any medications: **[ ] yes** **[ ] no**

Specify if yes_____

2) Any calcium / vitamin D supplementation: **[ ] yes** **[ ] no**

3) Habits: [ ] Alcohol [ ] Smoking [ ] Tobacco [ ] Others

specify _____

4) Any previous hospitalization: **[ ] yes** **[ ] no**

specify if yes: _____

5) Any chronic diseases:

[ ] Diabetes mellitus

[ ] Hypertension

[ ] Epilepsy

[ ] Chronic kidney disease on dialysis

[ ] Malignancy

[ ] Rheumatoid arthritis

[ ] Psoriasis

6) Diet- **[ ] Veg [ ] Mixed**

7) Milk consumption **[ ] Yes [ ] No**

if yes how much_____

8) Back pain or any spinal deformities [ ] Yes [ ] No

9) H/o of any fractures due to minor trauma [ ] Yes [ ] No

- **Special Investigations:**

T SCORE	INFERENCE

SERUM HOMOCYSTIENE	INFERENCE

WHO Criteria for 'T' score

Normal : 'T' score at or above -1 SD

Osteopenia : 'T' score between -1 to -2.5 SD

Osteoporosis : 'T' score at and above -2.5 SD

Normal Serum Homocysteine = 5-15 micromoles mcmol/L

ANNEXURE -IV PHOTOGRAPHS

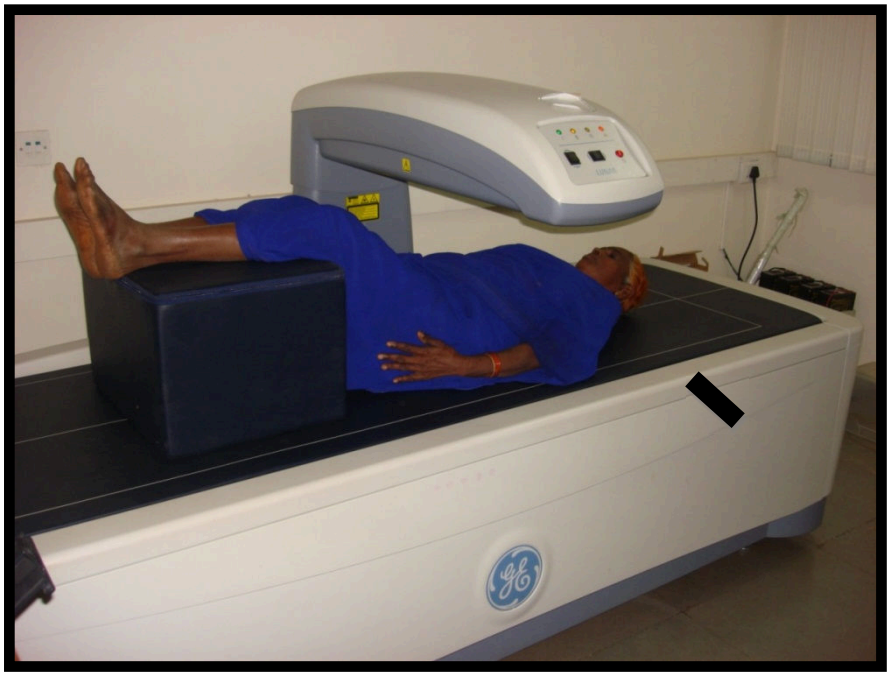
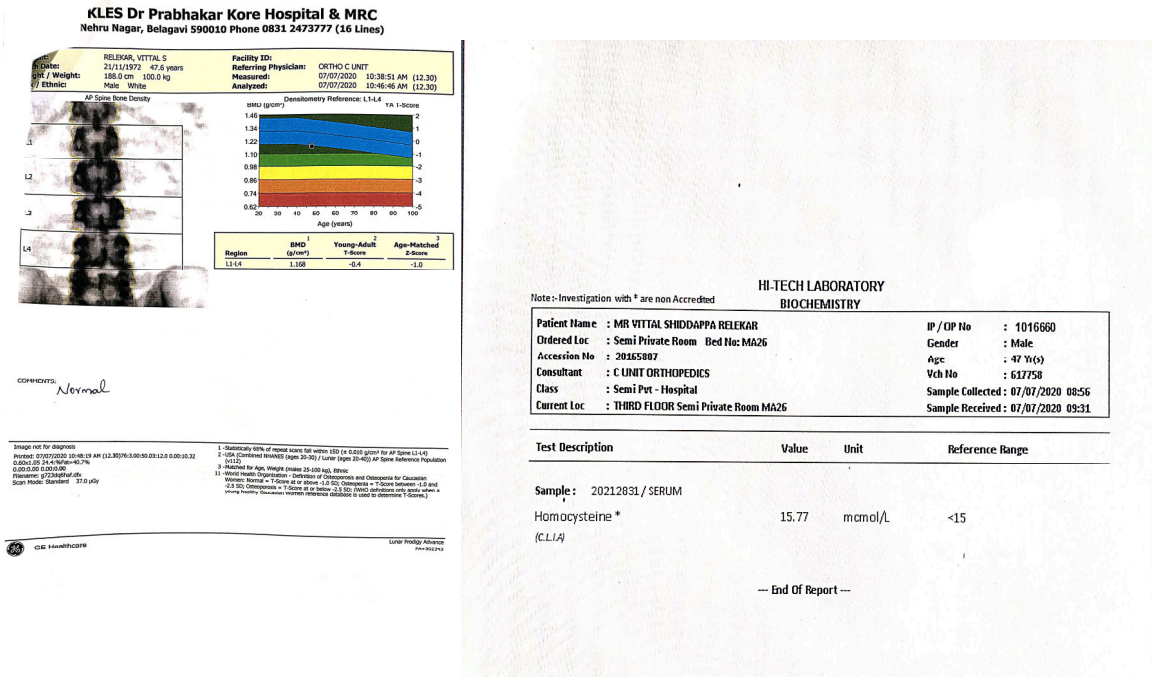


Figure 2: DEXA scan of lumbar spine



KLES Dr Prabhakar Kore Hospital & MRC
Nehru Nagar, Belagavi 590010 Phone 0831 2473777 (16 Lines)

RELEKAR, VITTAL S
21/11/1972 47.6 years
188.0 cm 100.0 kg
Male White

Facility ID:
Referring Physician: ORTHO C UNIT
Measured: 07/07/2020 10:38:51 AM (12.30)
Analyzed: 07/07/2020 10:46:46 AM (12.30)

AP Spine Bone Density
Densitometry Reference: L1-L4

Region	BMD (g/cm²)	Young-Adult T-Score	Age-Matched Z-Score
L1-L4	1.168	-0.4	-1.0

COMMENTS: Normal

HI-TECH LABORATORY
BIOCHEMISTRY

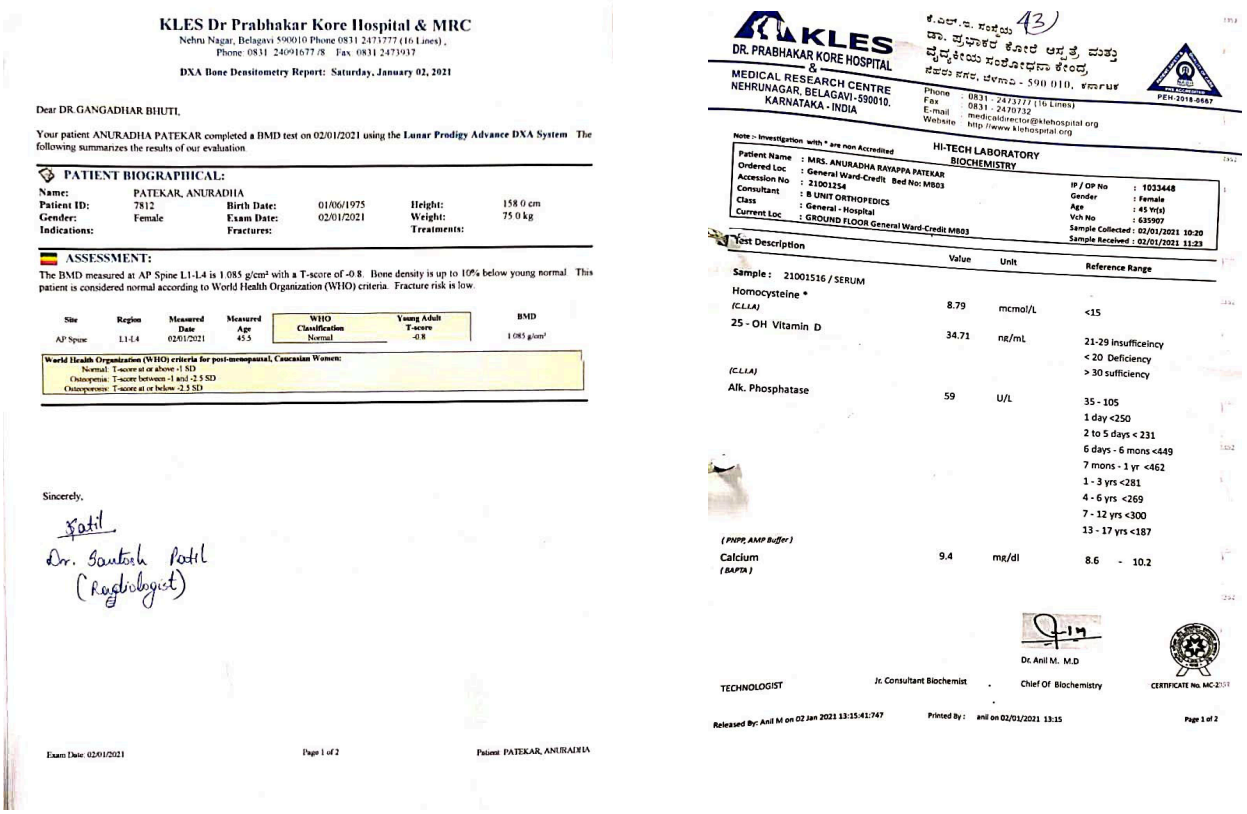
Note :-Investigation with * are non Accredited

Patient Name	: MR VITTAL SHIDDAPPA RELEKAR	IP / OP No	: 1016660
Ordered Loc	: Semi Private Room Bed No: MA26	Gender	: Male
Accession No	: 20165807	Age	: 47 Yr(s)
Consultant	: C UNIT ORTHOPEDICS	Vch No	: 617758
Class	: Semi Pvt - Hospital	Sample Collected	: 07/07/2020 08:56
Current Loc	: THIRD FLOOR Semi Private Room MA26	Sample Received	: 07/07/2020 09:31

Test Description	Value	Unit	Reference Range
Sample : 20212831 / SERUM			
Homocysteine * (C.L.I.A)	15.77	mcmol/L	<15

--- End Of Report ---

Master Chart : sample number 26



KLES Dr Prabhakar Kore Hospital & MRC
Nehru Nagar, Belagavi 590010 Phone 0831 2471777 (16 Lines) ,
Phone 0831 2409167 /8 Fax 0831 2473937

DXA Bone Densitometry Report: Saturday, January 02, 2021

Dear DR GANGADHAR BHUTI,

Your patient ANURADHA PATEKAR completed a BMD test on 02/01/2021 using the Lunar Prodigy Advance DXA System The following summarizes the results of our evaluation

PATIENT BIOGRAPHICAL:

Name:	PATEKAR, ANURADHA				
Patient ID:	7812	Birth Date:	01/06/1975	Height:	158.0 cm
Gender:	Female	Exam Date:	02/01/2021	Weight:	75.0 kg
Indications:		Fractures:		Treatments:	

ASSESSMENT:

The BMD measured at AP Spine L1-L4 is 1.085 g/cm² with a T-score of -0.8. Bone density is up to 10% below young normal. This patient is considered normal according to World Health Organization (WHO) criteria. Fracture risk is low.

Site	Region	Measured Date	Measured Age	WHO Classification	Young Adult T-score	BMD
AP Spine	L1-L4	02/01/2021	45.5	Normal	-0.8	1.085 g/cm²

World Health Organization (WHO) criteria for post-menopausal, Caucasian Women:
Normal: T-score at or above -1 SD
Osteopenia: T-score between -1 and -2.5 SD
Osteoporosis: T-score at or below -2.5 SD

Sincerely,

Dr. Santosh Patil
(Radiologist)

Exam Date: 02/01/2021 Page 1 of 2 Patient: PATEKAR, ANURADHA

KLES
DR. PRABHAKAR KORE HOSPITAL
&
MEDICAL RESEARCH CENTRE
NEHRUNAGAR, BELAGAVI-590010.
KARNATAKA - INDIA

ಕ.ಎಲ್.ಇ. ಸಂಸ್ಥೆಯ 43
ಡಾ. ಪ್ರಭಾಕರ ಕೋರೆ ಆಸ್ಪತ್ರೆ ಮತ್ತು
ವೈದ್ಯಕೀಯ ಸಂಶೋಧನಾ ಕೇಂದ್ರ,
ನೆಹರು ನಗರ, ಬೆಳಗಾವಿ - 590 010, ಕರ್ನಾಟಕ

Phone : 0831 - 2473777 (16 Lines)
Fax : 0831 - 2470732
E-mail : medicaldirector@klehospital.org
Website : http://www.klehospital.org

PEH-2018-5687

Note :- Investigation with * are non Accredited

HI-TECH LABORATORY
BIOCHEMISTRY

Patient Name	: MRS. ANURADHA RAYAPPA PATEKAR	IP / OP No	: 1033448
Ordered Loc	: General Ward-Credit Bed No: MB03	Gender	: Female
Accession No	: 21001254	Age	: 45 Yr(s)
Consultant	: B UNIT ORTHOPEDICS	Vch No	: 635907
Class	: General - Hospital	Sample Collected	: 02/01/2021 10:20
Current Loc	: GROUND FLOOR General Ward-Credit MB03	Sample Received	: 02/01/2021 11:23

Test Description	Value	Unit	Reference Range
Sample : 21001516 / SERUM			
Homocysteine * (C.L.I.A)	8.79	mcmol/L	<15
25 - OH Vitamin D (C.L.I.A)	34.71	ng/mL	21-29 insufficeincy < 20 Deficiency > 30 sufficiency
Alk. Phosphatase (PNPP, AMP Buffer)	59	U/L	35 - 105 1 day <250 2 to 5 days < 231 6 days - 6 mons <449 7 mons - 1 yr <462 1 - 3 yrs <281 4 - 6 yrs <269 7 - 12 yrs <300 13 - 17 yrs <187
Calcium (BAPTA)	9.4	mg/dl	8.6 - 10.2

Dr. Anil M. M.D
Chief Of Biochemistry

TECHNOLOGIST Jr. Consultant Biochemist

CERTIFICATE No. MC-2157

Released By: Anil M on 02 Jan 2021 13:15:41:747 Printed By : anil on 02/01/2021 13:15 Page 1 of 2

Master Chart : sample number 47

Figure 3 : DEXA Score and Serum Homocysteine Levels

ANNEXURE -V MASTER CHART

Date	IP/OP No.	Patient id	Gender	Age	AP Spine Tscore	BMD	Interpretation	Sr. Homocystiene
1/14/2020	1001025	7759	male	47	-0.3	1.179	Normal	13.2
1/16/2020	1001050	7760	male	54	-3.5	0.464	Osteoporosis	64.3
1/20/2020	1001056	7710	male	69	-1.8	1.003	Osteopenia	48.32
1/24/2020	1001068	7715	female	67	-3.9	0.464	Osteoporosis	68.4
1/26/2020	1001093	7758	male	44	-0.13	1.028	Normal	4.9
1/27/2020	1001150	7782	male	61	-2.3	0.945	osteopenia	25
1/30/2020	1001189	7786	male	47	-0.5	1.279	Normal	5.1
1/30/2020	1001250	D-7871	male	58	-2.2	0.952	osteopenia	33.2
2/4/2020	1001001	7877	male	56	-1.7	1.061	Osteopenia	51.71
2/7/2020	1001015	7873	female	52	-0.5	1.263	normal	5.6
2/10/2020	1001060	7881	male	48	-0.7	1.132	osteopenia	27.7
2/15/2020	1002010	7891	male	56	-0.4	1.279	normal	6.2
2/19/2020	1002065	7897	male	44	0.2	1.249	normal	5.3
2/19/2020	1002095	7898	male	69	-1.4	1.052	Osteopenia	27.96
2/19/2020	1002174	7893	male	70	0.7	1.308	normal	5.3
2/22/2020	1002198	7897	male	66	-2.6	0.464	Osteoporosis	56.7
2/29/2020	1004279	7906	female	68	-2.8	0.842	Osteoporosis	60.21
3/2/2020	1004220	7908	female	48	-1.2	1.04	Osteopenia	33.8
3/1/2020	1004252	7907	female	70	-2.6	0.865	Osteoporosis	46.9
3/3/2020	1004532	7909	male	44	-0.5	1.157	Normal	8.3
3/10/2020	1004635	7920	female	63	-3.2	0.064	Osteoporosis	93
3/14/2020	1006839	7925	female	46	-3.6	0.744	Osteoporosis	44.4
3/14/2020	1006910	D-7926	female	68	-4.1	0.687	Osteoporosis	78.9
3/17/2020	1007512	D-7931	female	59	-1.7	0.981	Osteopenia	11.87
7/2/2020	1007890	7961	female	47	0	1.178	normal	5.3
7/7/2020	1017214	D-7963	male	47	-0.4	1.168	normal	5.3
7/7/2020	1017814	7964	male	70	-1.2	1.079	osteopenia	7.62
7/8/2020	1018066	7966	male	55	-1.4	1.75	osteopenia	13.54
7/9/2020	1016272	D-7967	male	59	-3.1	1.59	Osteoporosis	64.2
7/17/2020	1018375	7969	male	38	-1.2	1.073	Osteopenia	8.49
8/6/2020	1024812	7778	male	62	-2.7	0.004	Osteoporosis	56.2
8/5/2020	1025008	7977	female	60	-1.9	2.011	osteopenia	19.8
8/10/2020	1025016	7779	male	70	-1	1.032	normal	8.68
8/17/2020	1025615	7780	female	64	-1.7	0.978	Osteopenia	24.8
8/27/2020	1026040	7783	male	53	0.3	1.257	Normal	7.34
8/31/2020	1026750	7787	male	69	-1.6	1.032	osteopenia	19.5
8/2/2020	1026708	7788	female	60	-2.9	0.837	Osteoporosis	42.49
8/2/2020	1026814	7789	female	55	0.4	1.6654	normal	8.41
8/4/2020	1026861	7794	male	59	-1.5	1.042	osteopenia	14.78
8/2/2020	1026802	7790	male	68	-1.3	1.069	osteopenia	21.54

8/2/2020	1026317	7791	male	65	-0.8	1.119	Normal	7.65
8/18/2020	1028224	7797	female	69	-5.4	0.528	Osteoporosis	45.55
8/25/2020	1028210	7804	female	67	-3.3	0.083	Osteoporosis	29.8
8/31/2020	1032435	7809	female	65	-5	0.578	Osteoporosis	34.6
8/30/2020	1032700	7810	female	58	-4.5	0.64	Osteoporosis	71.33
8/31/2020	1032650	7809	female	58	-5	0.578	Osteoporosis	82.4
9/1/2020	1033448	7812	female	45	-0.8	1.085	Normal	8.79
9/4/2020	1033584	7815	female	67	-3.1	0.824	Osteoporosis	13.35
9/6/2020	1033560	7817	female	59	-1.5	0.997	osteopenia	16.43
9/9/2020	1034431	7819	female	70	-3.1	0.805	Osteoporosis	33.74
9/11/2020	1034460	7821	female	68	-3.8	0.729	Osteoporosis	45.6
9/13/2020	1034498	7824	female	56	-1.4	1.015	Osteopenia	18.6
9/15/2020	1034018	7826	female	48	-0.8	1.032	Normal	6.2
9/17/2020	1034025	7818	female	53	-0.2	1.151	Normal	7.28
9/22/2020	1034080	7955	female	55	-2.4	0.887	Osteoporosis	19.23
9/24/2020	5955265	7957	female	56	-1.9	0	Osteopenia	18.21
10/2/2020	1035058	7821	female	53	-3.4	0.77	Osteoporosis	11.8
10/7/2020	1035700	7832	male	36	-1.8	1.002	Osteopenia	34.5
10/10/2020	1036590	7837	male	38	-1.8	1.008	Osteopenia	33.58
10/14/2020	1037185	7839	male	37	-0.6	1.147	Normal	16.83
10/18/2020	1372000	7849	female	49	-1.8	0.962	Osteopenia	14.34
10/21/2020	1038404	7851	female	51	-1.8	0.967	Osteopenia	13
10/25/2020	1041437	7877	female	59	-2.1	0.929	Osteopenia	11.68
10/28/2020	1042789	7879	female	64	-3.2	0.799	Osteoporosis	24.58
10/29/2020	1043605	7883	male	68	-1.8	1	Osteopenia	17.94
10/30/2020	1043750	D7866	male	58	-0.6	1.143	Normal	14.3
10/30/2020	1047411	7893	female	51	-0.9	1.072	Normal	16.07
11/4/2020	1047420	7892	female	49	-2.6	0.866	Osteoporosis	27.5
11/12/2020	1047450	7000	male	52	-1.3	1.069	osteopenia	15.7
11/14/2020	1050097	7906	male	54	-0.9	1.111	Normal	8.54
11/16/2020	1055601	7907	male	42	-0.4	1.174	Normal	13.2
11/19/2020	1055611	7910	male	61	-2.3	0.945	Osteopenia	26.93
11/21/2020	1055620	7920	female	44	-0.7	1.11	Normal	6.54
11/22/2020	1055680	7922	male	68	-3.4	0.789	osteoporosis	58.2
11/24/2020	1055710	7939	female	64	-2.8	0.839	osteoporosis	47.45
12/2/2020	1055750	7960	male	41	-0.8	1.032	normal	6.8
12/10/2020	1055790	7969	male	69	-2.3	0.958	osteopenia	23.21
12/12/2020	1055830	7971	male	56	-2.1	0.922	osteopenia	21.78
12/16/2020	1055880	7990	female	42	-0.2	1.82	normal	8.9
12/18/2020	1055920	7999	female	66	-2.5	0.833	Osteoporosis	37.3