Scandic Journal of Advanced Research and Reviews

ISSN: 2703-965X CODEN (USA): SJARCA

Cross Ref DOI: dx.doi.org/10.55966/sjarr

Journal homepage: www.sjarr.com

Determinition of Bone Strength by Using Procollagen Type 1 N-Terminal Propeptide (P1NP) as a Predictive Marker in Native Population of Pakistan.

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Scandic Journal of Advanced Research and Reviews, 2023, 4(01), 001–031

Publication history: Received on 19 December 2022; revised on 15 January 2023; accepted on 20 January 2023

Article DOI: https://doi.org/10.55966/sjarr.2023.4.1.0058

Abstract

Introduction: Due to better health facilities, food and living facilities the life expectancy is increasing which is leading towards Osteopenia and Osteoporosis in the whole world. Despites of its prevalence it is ignored in Pakistan due to which it is causing a burden on Pakistan economy. It is therefore necessary to find some suitable

methods for the quick identification of the problems so that people will be safe from the cost of treatment of the fractured bones and they are treated before going to worse situation. Vigorous physical activity in adults have a great impact bone mass and bone turnover. The effects of moderate activity (physical) remain tentative. Bone formation marker propertied of type 1 Procollagen (P1NP) is related to physical activity and its levels. The relationship between P1NP and physical activity remained significant after the adjustment of data by two factors, age and BMI (body mass index). In Pakistan, use of P1NP for the early identification of bone strength is not implemented yet.

Objectives: The key purpose of this research is to explore that either P1NP is used to indicate the early bone strength indicator as compared to BMD in Pakistani population or not.

Research Plan its Implementation Strategies: In addition to BOOT camps, clinical research was held at the same time in the department of physiology at JPMC, BMSI-Karachi.

Procedures: 80 participants having osteopenia with BMD ranges from -0.9 to -1.95 SD registered themselves for sample donation. They were divided in to two groups. Group A that was non-exercising or control group and the other one was group B or exercising group randomly after getting their written informed willingness, each having 40 participants. For collecting best quality data from them, a questionnaire was conducted. Blood samples for P1NP, were obtained from each individual participant and by using Enzyme- linked immunosorbent assay (ELISA) The analysis of all the blood samples were carried out at baseline, 3rd and 6th month. For the evaluation of BMD at a, Quantitative Ultrasound all three levels, technique was used. By using SPPS 22 Software program, analysis of all the collected data was accomplished

Outcomes of Research: The research results that we obtained, was showing clearly that the average life span of group B was 27.93±3.94 years having p value of (p=0.05) while 27.99±3.94 years for the control group A. Out of these, females constitute about 69.6% of the total number of participants. We got different results of PNIP before, mid and after the research. These were (41.34±16.97) ng/ml vs. (41.54±17.98) ng/ml, p = 1.68) before starting the training, at mid training was (40.97±16.98) ng/ml vs. (56.91±14.93) ng/ml, p = 0.002) at mid and (41.82±16.93) ng/ml vs. (62.046±13.53)

ng/ml, p = 0.003) after the training. We obtained following results -1.9217±0.265, 1.9217±0.265 and -1.9043±0.259 at the base, mid and the training for BMD (T-Score) in the control group A. In interventional group. The mean value of BMD (T-Score) for exercising or B group was -1.9283±0.350, -1.9091±0.331 and -1.6075±0.3886 at the baseline, mid and after the training respectively. The value of P1NP in group A and group B was changed to 0.33% and 45.84% respectively. On the other hand the BMD (T-Score) value was changed to 0.91% and 16.64% for A and B groups respectively.

Conclusion: From the observation of our research, we determined that there was significant increase in levels of P1NP in group B while the improvement in the value of BMD according to T-Score was slower in interventional group than control group. So, it was concluded that P1NP is better than BMD for the early determination of bone strength.

Key Words: Osteopenia, young adult, Bone mineral density, Osteoporosis, adult, Exercise, PNIP

PURPOSE OF STUDY

The main purpose of our study is to find new cost-effective methods for the early detection of bone strength so that the people from the whole world would be safe from the worst outcomes of osteoporosis. By using preventive measures and effective therapeutic methods we can increase the life expectancy and the heavy cost of the treatment.

PATHOPHYSIOLOGY

When there is a failure in the coupling of the mechanism of resorption and osteoblast then result in the loss of body mass and this condition is known as Osteopenia. Both men and women have their strongest bones in their early thirty's. after the age of 30s the skeletal bones weakness start and continue throughout life, and the bone resorption dominates (Babbar, Sharma, Jain, & Gupta, 2022).

OVERVIEW OF TOPIC

Osteoporosis is ignored in Pakistan due to burden in economy which is causing a lot of health issues like, data unavailability, polio, lack of specific guidelines for doctors

(Mithal, Bansal, Kyer, & Ebeling, 2014). Any imbalance in the bone remodeling process result in the abnormal bone homeostasis which is the leading cause of osteopenia which progress to osteoporotic problems. Osteopenia is very prevalent in Pakistan in young age. one of the research conducted in Karachi shown that Osteopenia percentage in females is 64% below 30 years and 55% below 45 years (Jaleel, Nasrullah, & Khan, 2010). The price of treatment and diagnosis is very high i despite the availability of number of methods for determination of bone mineral density. Bone turnover markers are another developing identifiers for identification of BMD. These markers are actually cellular constituent of bone matrix which are present in urine and blood. Bone turnover markers are of two types bone resorption markers like NTX and CTX and bone formation markers like P1CP, PINP Osteocalcin. A bone turnover marker is preferred as compared to DXA is due to its better patient compliance, low cost, and better treatment monitoring (Shetty, Kapoor, Bondu, Thomas, & Paul, 2016).

Different techniques for bone health assessment

To study osteoporosis, the serum P1NP is used as a bone strengthening biomarker due to its number of advantages, like it is stable at room temperature, variable circadian rhythm, and insensitivity to dietary intake (Garnero, 2017).

Bone consists of two components both inorganic and organic. Organic bone matrix contain type 1 collagen. Procollagen is produced from fibroblast and osteoblast cells which contain C and N terminals. During process of collagen formation from Procollagen proteases enzymes cleave the terminals. P1NP shows type 1 collagen deposition because it is type 1 Procollagen and is conjugated onto bone matrix. it is released into blood stream (Kuo & Chen, 2017). It has trimetric structure when released but changed to monomeric when heated. Radioimmunoassay or ELISA are usually used to determine P1NP trimetric structure. It is a very hypersensible marker for bone formation in osteoporosis and clinically used. As it shows low intra-individual variability, exact testing and little diurnal change it probably respond to therapy. We cannot use it for screening (Townsend, 2016).

Bone Mineral Density Techniques

DXA is considered as gold standard by Who because of its many advantages but its main disadvantage is that in involves ionizing radiations and it only do the evaluation of bone in two dimension providing analysis of only bone density at the spot but due to its rare availability and high cost limits it's use in Pakistan primary (Cheriyan, Haridas, & Reshma, 2018). QCT (Quantitative Computed Tomography) measures volumetric BMD. Three dimensional structure, but involves high radiations (Adams, 2009). "QUS (Quantitative Ultrasound)" is used for the evaluation of instability and morphology of the bones. It can independently forecast fracture risk. It is free from radioactivity, economical, consistent, portable, and easy to use. It can be used in the absence of DXA and for people with less mobility and uncooperative behavior. But it has certain limitations like intra-observer and inter-observer variability (Saito et al., 2016).

Quantitative Ultrasound (QUS) verses other techniques for Bone Mineral Density

The Characteristics of bones such as microstructure and elasticity ate determined by QUS but such information could not be obtained from DXA. Trabecular architecture is very important for the determination of bone strength. Both QCT and DXA are used to measures BMD which depends only on bone density and is independent on bone structure. "Quantitative ultrasound (QUS) techniques" is used to assess the factors involves in the deformation of bones in comparison to its density as well as its strength, which are used to change the acoustic factors (Link & Kazakia, 2020).

Bone Turnover Marker (P1NP) verses Bone Mineral Density Test

DXA test besides its number of advantages it has some limitations too such as less availability, high cost, poor sensitivity to locate future fractures and bone strength determination. The bone turnover markers are preferred over DXA because it is used to determine the variation in the metabolism of bones earlier than DXA and it can be repeated after very short interval. Besides this DXA provides information about total bone loss on the other hand bone turnover marker are used for the prognosis of situation related to the remodeling process of bones as well as their identification. The bone turnover marker has many advantages over the DXA due to its good way of monitoring, low cost and better patient compliance. QUS limitations such as observer unpredictability, while its consistency is influenced by random variations including

core temperature of heel, equipment drift, location of heel in the beam of ultrasonication, and width as well as the characteristics of the nearby soft tissue. Bone turnover marker on the other hand free from such limitations therefore it is better than quantitative ultrasound by heel densitometry (Wei et al., 2021).

OPERATIONAL DEFINITIONS

According to the criteria set by WHO (2007), "Osteopenia is defined as bone density lying between 1and 2.5 SD below the young adult (a T score between -1 to -2.5 SD)."

P1NP

For checking the effectiveness of osteoporosis, the most sensitive and specific marker is type 1 precollegen having amino terminal propetide.

Here is the new reference range values at Spectrum Health center for P1NP

Young individual having age 18 or above: 23-93 mcg/L

And these reference range values are very similar to the reference ranges that was observed in Mayo Medical Laboratories:

Young male: 22-87 mcg/L
Adult female premenopausal: 19-83 mcg/L
Adult female postmenopausal: 16-96 mcg/L

(https://lab.spectrumhealth.org/2019/06/12/p1np-update/#:~:text=The%20new%20reference%20range%20is,%3A%2016%2D96%20mcg%2FL)

HYPOTHESIS

In the population of Pakistan living in local area P1NP is early pre identifying marker for determining the bone strength as compared to BMD.

METHODS AND PARITICIPANTS

STUDY DESIGN:

The study design is Interventional.

RESEARCH SETTING:

In the Department physiology of the Basic Medical Sciences Institute (BMSI) along with Boot camp under the supervision of Prof. Dr. Nargis Anjum the research study was conducted.

DURATION OF STUDY:

In the duration started from September 2021 to March 2022 research was conducted.

SAMPLE SIZE

For the RCT, 80 participants were selected which were divided into control and exercising group each containing 40 participants. After the 10% attrition in the participants lost to follow up, the final number of participants in the sample size was 92 after rounding off so both groups contain 46 participants each.

The main purpose of selecting these participants is to find the comparison of P1NP levels in exercising and non-exercising groups. Selection of sample is dependent upon the quantity of P1NP in the exercising and non-exercising participants that Adami et al. (2008) reported. By using online tool, the proper sample size was determined through mean difference that has been authorized (Openepi.com). With the power at 80% and 5% alpha level set, same formula was applied.

Recruitment of Subjects

From Boot (exercise) camp "BURNOUT 40", almost 92 participants were selected after the selection criteria. All individuals were recommended and their consent was taken and they were randomized in the following groups.

GROUP A: with Osteopenia (Non-Exercising Group) having 9 BMD between -0.9 to -1.95 SD.

GROUP B: with Osteopenia (Exercising Group) having BMD value between -0.9 to -1.95 SD.

RESEARCH POPULATION

The participants for research were males and females with osteopenia and having age ranges from 20-40 years.

SAMPLING TECHNIQUE:

The technique used for sampling was non-probability successive technique.
In this research sampling technique was successive. All of the participants were eligible and available consecutively at the spot was chosen for the research for this boot camp was recruited in an easily available area of Karachi.

TECHNIQUE FOR RANDOMIZATION

Participants were selected on random bases into two groups i.e. exercising and non-exercising.

This study will follow Simple randomization using open epi.com open source online random number generator to form 2 groups of sedentary individuals with osteopenia' namely control group and exercise group. A group of 46 individuals who will start a boot camp exercise training 6 month later will be labeled as sedentary group.
Sedentary control person will be identified through the reference from our available potential boot camp participants. With their written informed consent they will be randomized to exercise and non-exercise group. The non-exercise group will be one who consented to join the boot camp six months later. With the consent of the host boot camp, 50% reduction in exercise program registration fee will be offered to individuals who will be randomized to the deferred-start, up to six months, group for the boot camp. The sedentary control referred by the active participants will be age and sex match. This would be an open label randomized trial and no blinding will be done. However there is little or no risk of bias since the method of ascertainment of bone mineralization are independent to the participant perception of the intervention. All the participants will receive an internationally accepted age appropriate guideline brochures / booklet for health promoting and healthy lifestyle at the end of research study.

SAMPLING CRITERIA

Criteria for inclusion: Age group 20-40 years, gender and inactive population with Osteopenia.

Criteria for exclusion:

Following samples were not included in the study,

Women who are pregnant or nursing, individuals with musculoskeletal disorders, a person with cancer, a person with liver and kidney problems, a person with comorbid conditions such as diabetes and hypertension, any person with a medical condition that would make exercise dangerous, Individuals who have undergone bone-altering surgery within six months of the study, those who have received radiation or chemotherapy, those who use medications that affect bone metabolism, those who are following a particular diet or exercise regimen, and those who decline to participate in the study.

STUDY PROTOCOL

Knowledgeable willingness

From all the participants we got the informed consent by telling them about the purpose of study. And the permission for the application is granted by JPMC's Institutional Review Board in Karachi.

Ethical Consideration:

The Jinnah Postgraduate Medical Centre's Institutional Review Board in Karachi was contacted using a letter with the number F.2-81/2021-GENL/67104/JPMC to obtain ethical permission. Extreme confidentiality was maintained when handling the data.

NO.F.2-81/2021-GENL/ 6704 /JPMC
JINNAH POSTGRADUATE MEDICAL CENTRE
KARACHI.75510.

Dated the 28/9 2021

Dr. Nasima Zafar
Department of Physiology, BMSI
JPMC, Karachi.

Subject: ***Application of procollagen type 1 N-terminal propeptide (PINP) as an early predictive marker of bone strength in local population of Pakistan.***

With reference to your application / letter dated 16th March, 2021, on the subject noted above and to say that the Institutional Review Board has approved your subject proposal.

Dr. Nausheen Rauf
Secretary Institutional Review Board Committee
JPMC, Karachi.

Copy forwarded for information and necessary action to:

- Dr. Nargis Anjum, Faculty of Medicine, University of Karachi, Karachi.
- Dr. Kousar Abbas, Assistant Prof. of Physiology, BMSI, JPMC, Karachi.

SAMPLE COLLECTION:

After aseptic venipuncture site cleaning, a roughly 10ml blood sample was taken from the patient's median cubital vein. First, each participant's unique ID was written on the tube labels. Blood was then transferred to a gold-topped vacutainer that included includes separating gel and clot activator in order to measure P1NP at the baseline, third, and sixth-month stages. Serum was obtained by centrifuging the vacutainer at 4000 rpm for 10 minutes.

The serum was transferred from the agarose separator into Eppendorf tubes using the same labelling as on the vacutainer, and these tubes were then maintained at -80°C until they were used for sample testing. With the use of an ultrasound heel densitometer and heel quantitative ultrasonography, the bone density was evaluated at the first, third, and sixth months. The patient was classified as either Normal, Osteopenia, or Osteoporosis based on the Bone Mineral Density. There were those with osteopenia included.

Data Collection Procedure:

All those people who attended boot camp or JPMC and fulfill the exclusion and inclusion and requirements was included in the research. Their informed consent was obtained after informing them about the purpose of the research. Besides getting their personal history information like (age, address, sex, name, socio economic , occupational, medical, marital status, educational, and drug history), laboratory testing such as bone mineral density and Procollagen type 1N- terminal Propeptide and density, anthropometric measures which include, body fat percentage, height, body mass index and weight, was documented on a specially designed form.

WHO has proposed guidelines on physical activity and sedentary behavior based on the synthetic proves under United States Physical Activity Guidelines Advisory Committee (PAGAC). Recommendation includes that Adult (aged 18-64 years) should do physical exercise on regular basis and they should have to engage themselves with at least of 150–300 minutes for aerobic exercise with moderate-intensity. They should also have to indulge themselves in muscular exercises which include all of the muscle groups twice or more a week.

After recruitment of participants in the respective groups all the participants were briefly explained about each exercise and its benefits included in training session. Importance of attending full 6 months session was emphasized to avoid maximum drop off. All exercises were done at night time.

At day 1 Bone mineral density, anthropometric measurements and blood sample were taken from all participants. From day 2 to day 5 acclimatization for all exercises were done as participants were sedentary before. We have moderate intensity exercise group the criteria for measuring exercise intensity was done by assessing overall heart rate through fitness tracker which every participants was wearing provided by boot camp. Assessing overall heart rate is the simply way to determine the intensity of exercise. Maximum heart rate MHR is the fastest heart rate with which anyone's heart can safely beat. Formula to find out anyone's maximum heart rate is:

MHR = 220 bpm - Age of Person

Everyone heart rate was mentioned while they were exercising through fitness tracker .Other alternative criteria for measuring exercise intensity includes Talk Test and Exertion Rating Scale. We used MHR for our study.

Highlights of Moderate Intensity Exercise performed at Camp

Intensity of exercise: Moderate intensity exercises

Type of exercises: Combination of Cardio (Aerobic), strength training (weight bearing) and stretch training.

Initial acclimatization period for participants: 4 days

Duration of exercise: 1 hour/5 days a week for 6 months

Every day pattern of adequate exercise performed at boot camp center

1 times x Warm-up circuit 250 skipping Ropes (8 min)		
Circuit NO.1	30x Burpees	12 min

Circuit NO.2 standing Mountain climbers, front n side jacks, elbow and knee, hop squats, power jack	3 sets x 15 count for each exercise	12 min
Circuit NO.3 Skipping rope, March n reach (free weight) reverse crunches press jacks, Boxing punches with squats, Taichi, High knee, pogos	(total number of 15 count for each exercise x3 sets	12 in
Circuit NO.4 Jump squats, planks, Lunges thrust press, Push up work, Butt kickers, Mountain climbers, Squat hold	3 sets x 25 secs for each exercise	12 min

After each circuit there was a break of two minutes.

At day 90 of exercise /boot camp we took second reading of Bone mineral density by heel densitometry and blood sample for P1NP from all participants. At day 180 of exercise /boot camp we took second reading of anthropometric measurements and third reading of Bone mineral density by heel densitometry and blood sample for P1NP from all the participating people.

Analysis of the results statistically

With SPSS version 22, statistical analysis was carried out. At alpha: = 0.5, the hypothesis was tested. The data were applied, calculated, analysed, and interpreted using the Chi-Square test for hypothesis testing. A paired t-test was utilised to compare the bone turnover marker between different times in time within the group. If

the data had a non-normal distribution, the mean, standard deviation (SD), and median (minimum and maximum) were reported. The level of statistical significance was set to p = 0.5 for the intention to treat analysis.

RESULTS

General characteristics of study participants

Table 4.1.

Evaluation of gender, age, marital status and profession in exercising and non-exercising groups

Measurement	Non exercising (Control group) (n=40)	Exercising (Interventional) (n=40)	Test -Statisitc	p-value
Age (years)			t-value	p-value
Age (Mean ± SD) years	27.99±3.94	27.93±3.94	0.54	0.053
Age range (year)	20-30	20-30		
Height (cm)			t-value	p-value
Height (cm)	166 ± 9.5	165 ± 9.5	0.52	0.052
Gender			Chi-Sqaure	p-value
Male (n=30)	15	15	0.000	0.053
Female (n=50)	30	30		
Marital Status			Chi-Sqaure	p-value
Married (n= 40)	20	20	0.59	0.052
Unmarried (n=40)	20	20		
Occupation			Chi-Sqaure	p-value
Indoor working (n=50)	25	25		
Outdoor working (n=30)	15	15	0.49	0.054

P1NP is a more accurate bone strength predictor than BMD, according to an ANOVA. It is associated with the level of physical activity. This association remained significant after adjusting the data (ANCOVA) by age, height, gender, marital status and occupation. In the parameter of age, no significant result is observed. The P-value

is greater than 0.05. Age, height and marital status showed P-values =0.052-0.054 which is indicating that the hypothesis is correct.

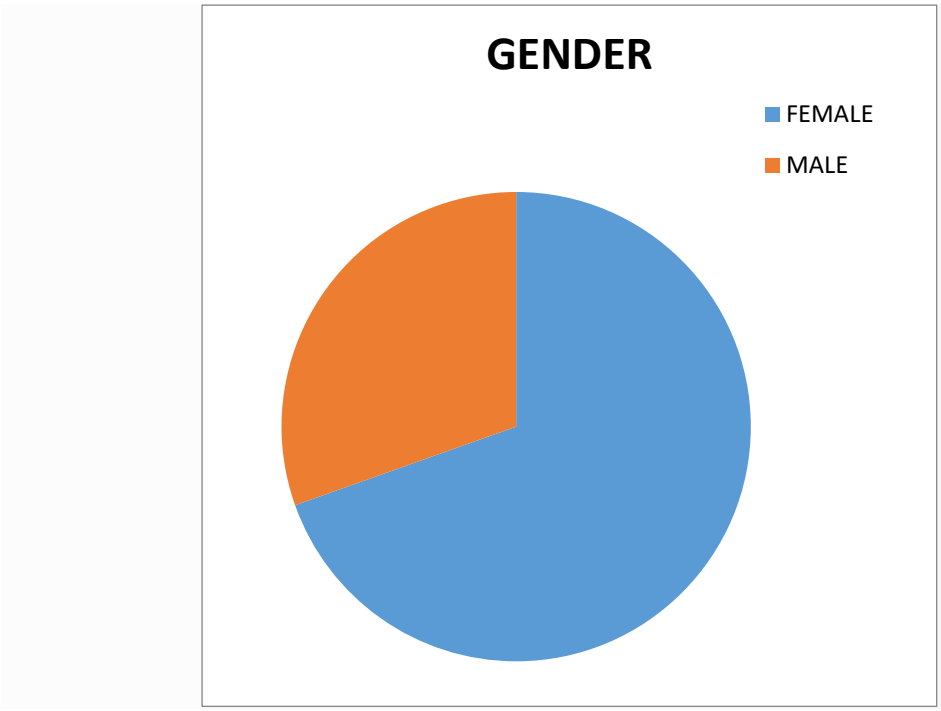

Figure 4.1. gender of the participants in the study

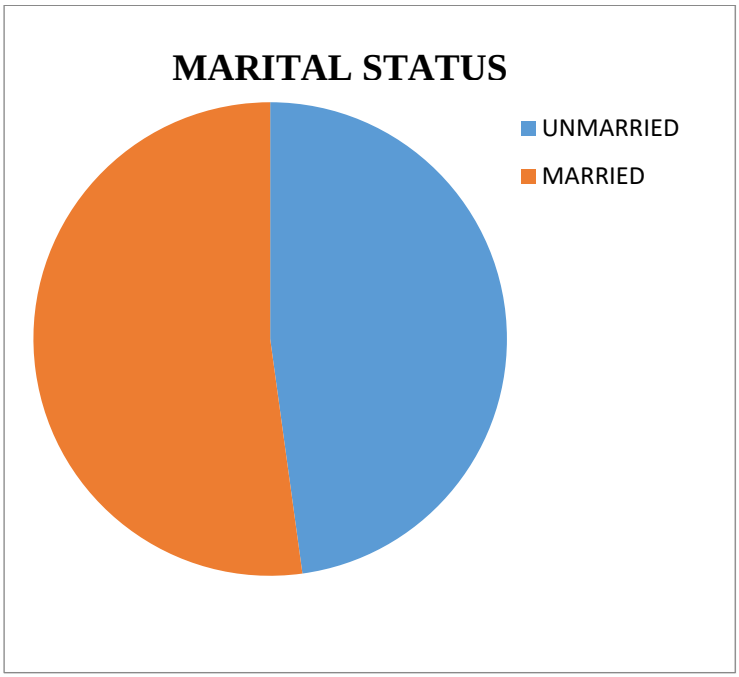

Figure 4.2. The individuals in the study's marital status

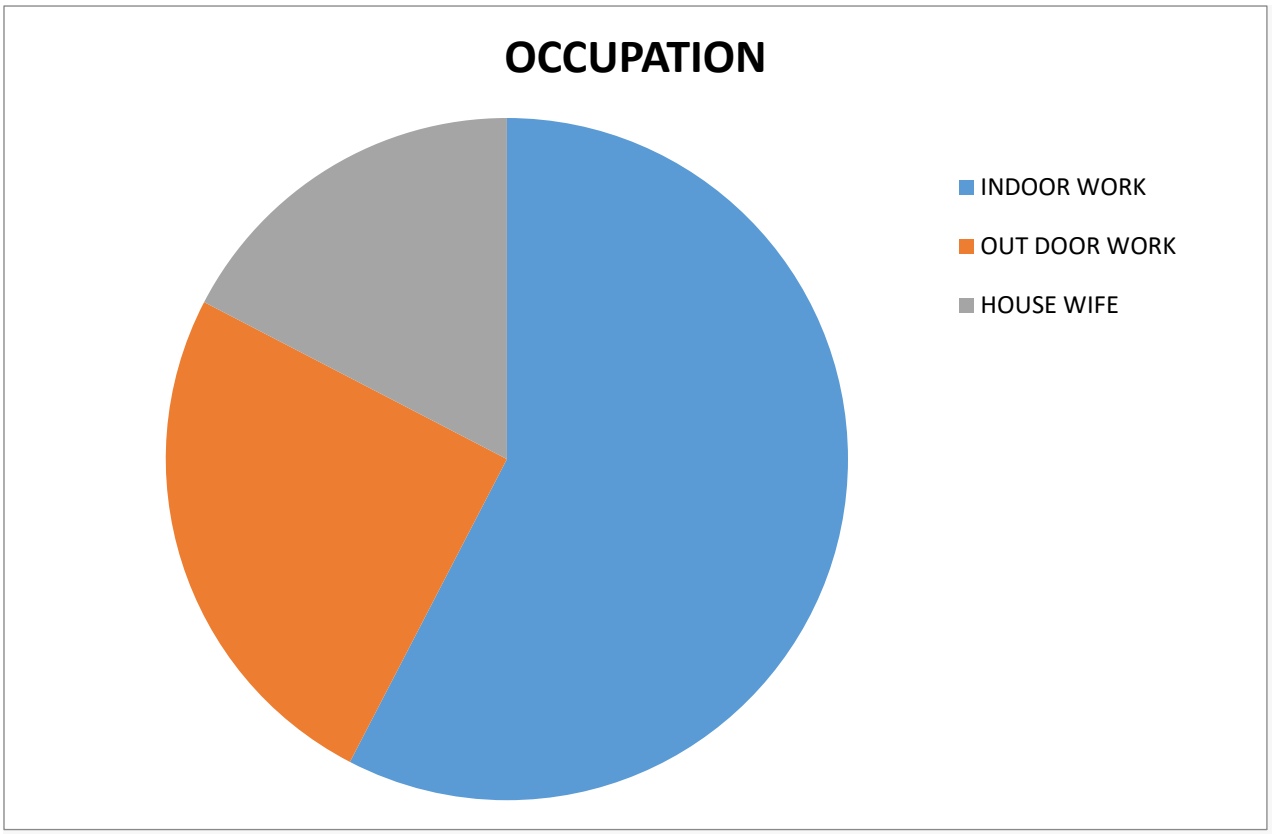

Figure 4.3. Participant's profession

Analyses of Study Participants' Anthropometric Data

Table 4.2. Evaluation of body weight between control group and interventional group

Groups	Statisitic	Body Weight (kg)		Mean of Difference (Kg)	t-value	p-value	95 % CI** of difference	
		Pre Training (Day-1)	Post Training (Day-90)				L..C.L	U.C.L
Non-Exercising (Control) Group) -A	N	46	46	1.504	7.034	0.001*	1.918	1.089
	Mean	85.56	84.06					
	± SD	14.14	13.80					
Exercising (Interventional) Group) - B	N	46	46	3.066	13.025	0.001*	2.592	3.539
	Mean	89.76	86.70					
	± SD	15.71	15.50					
Group-A vs Group-B	t-value	1.348	0.862					
	p-value	0.181	0.391					

The mean values of the observations before and after training, and their mean changes for both the control and the active groups are listed in table 4.2. According to the t-values, it is obvious that the results are according to the expectations. The level of variance is low which supports the hypothesis that P1NP is an early predictive marker of bone strength than BMD. * is significant difference and ** is confidence interval

Table 4.3. Comparison of Body Fat (%) in control and interventional group

Groups	Statisitic	Body Fat (%)		Mean of Difference Body Fat (%)	t-value	p-value	95 % CI** of difference	
		Pre Training (Day-1)	Post Training (Day-90)				L.C.L	U.C.L
Non-Exercising (Control) Group) - A	N	46.000	46.000	0.565	0.485	0.630	-2.914	1.783
	Mean	42.011	42.577					
	± SD	12.277	10.684					
Exercising (Interventional) Group) - B	N	46.000	46.000	3.104	17.139	0.001*	2.659	3.368
	Mean	41.477	38.463					
	± SD	9.768	9.848					
Group-A vs Group-B	t-value	0.231	1.92					
	p-value	0.818	0.058*					

P1NP levels grew significantly more quickly in the intervention group than in the control group, while the intervention group's BMD (T-Score) value showed only little improvement. The P-value of group A in comparison with group B is 0.005 which is most significant.

Table 4.4. Comparing Body Mass Index (kg/m-sq) in exercising and non-exercising group

Groups	Statistic	Body Mass Index (kg/m-sq)		Mean of Difference (kg/m-sq)	t-value	p-value	95 % CI** of difference	
		Pre Training (Day-1)	Post Training (Day-90)				L.C.L	U.C.L
Non-Exercising (Control) Group) -A	N	46	46	0.819	4.633	0.001*	0.463	1.175
	Mean	31.063	30.244					
	± SD	5.649	5.486					
Exercising (Interventional) Group) - B	N	46	46	1.304	6.192	0.001*	0.879	1.728
	Mean	32.009	30.705					
	± SD	5.791	5.525					
Group-A vs Group-B	t-value	1.348	0.042*					
	p-value	0.181	0.688					

The results indicated that if a patient seems to have a greater than average muscle content, it may be worth measuring body fat percentage and not treating based on BMI.

Comparison of BMD among different groups in different intervals

Table 4.5. Comparison of T-Score between control and interventional groups

Groups				
Non-Exercising (Control) Group) -A	Statistic	T- Score Pre-training (baseline)	T-Score Mid-training (3rd month)	T- Score Post-training (6th month)
Exercising (Interventional) Group) - B	n	40	40	40
	Mean	-1.82	-1.75	-1.78
	±SD	0.3	0.3	0.3
Group-A vs Group-B	n	40	40	40
	Mean	-1.7	-1.7	-1.60
	±SD	0.34	0.33	0.38
Statistic	t-value	0.13	0.21	3.5
	p-value	0.89	0.84	0.001*

	Non-Exercising (Control) Group-A			Exercising (Interventional) Group-B		
n	Pre -Mild Training	Mild-Post Training	Pre-post Training	Pre -Mild Training	Mild-Post Training	Pre-post Training
Mean of difference	40	40	40	40	40	40
t-value	-0.02	-0.09	-0.12	-15.7	-4.3	-20.5
p-value	2.3	4.2	4.3	12.9	9.99	14.8
95 % L.C.L	0.015*	0.001*	0.001*	0.001*	0.001*	0.001*
95 % U.C.L.	-0.064	-0.15	-0.205	-19.690	-5.278	-25.445
*** : Significant difference**	-0.007	-0.056	-0.073	-14.708	-3.621	-19.692

**L.C.I/U.C.I: Confidence Interval

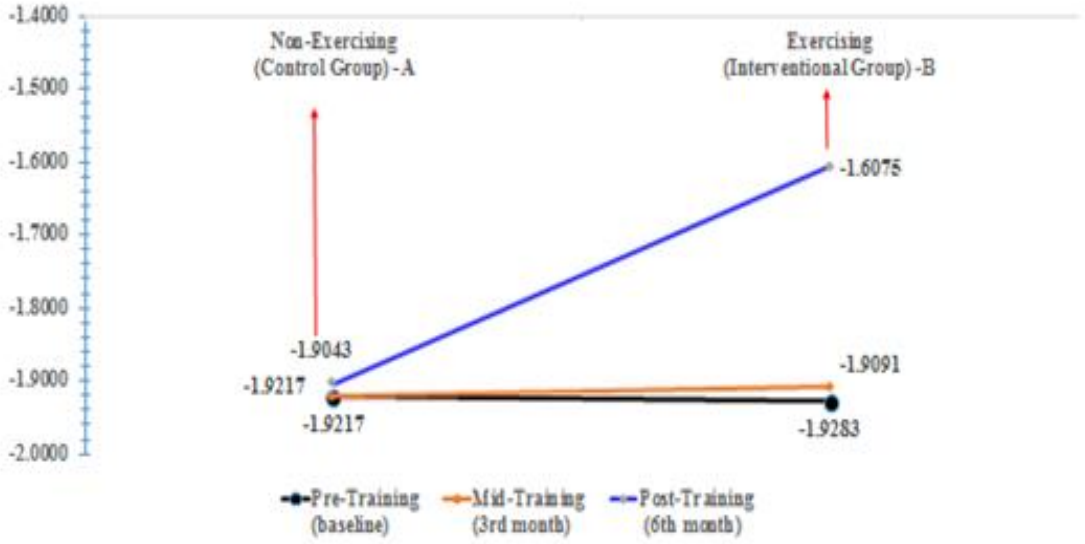

Figure 4.4. T-score comparisons between the non-exercising (control) and exercising (interventional) groups at the pre-, mid-, and post-training (6th month) points.

The BMD (T-Score) values in the control sample were -1.92170.265 at baseline, -1.92170.265 at mid-training, and -1.90430.259 at the end of training. BMI and body fat percentage cannot be maintained by physical activity alone, although it can lower the population's risk of being overweight and having a high body fat percentage.

Table 4.6. Comparison of Procollagen Type 1 N-Terminal (P1NP) (ng/dl) in Non- exercising (Control) and Exercising (Interventional) Groups

Groups	Statisitic	P1NP (ng/dl)		
		Pre Training (Baseline)	Mid Training (3rd month)	Post Training (6th month)
Non-Exercising (Control) Group) -A	n	40	40	40
	Mean	39.4	39.47	39.58
	± SD	15.93	16.91	16.81
Exercising (Interventional) Group) - B	n	40	40	40
	Mean	40.5	57.5	60.4
	± SD	17	14.9	14.5
Group-A vs Group-B	t-value	0.19	4.9	5.6
	p-value	0.678	0.001*	0.001*

* : Significant

**Confidence

Interval

Statistic	Non-Exercising (Control) Group-A			Exercising (Interventional) Group-B		
	Pre Training -Mild	Mild-Post Training	Pre-post Training	Pre Training -Mild	Mild-Post Training	Pre-post Training
N	40	40	40	40	40	40
Mean of difference	-0.026	-0.12	-0.13	-16.3	-3.95	-21.6
t-value	2.6	3.7	3.94	12.9	11	14.9
p-value	0.015*	0.001*	0.001*	0.001*	0.001*	0.001*
95 % L.C.L	-0.05	-0.12	-0.28	-17.6	-5.3	-23.4
95 % U.C.L.	-0.01	-0.05	-0.06	-13.8	-2.92	-18.5

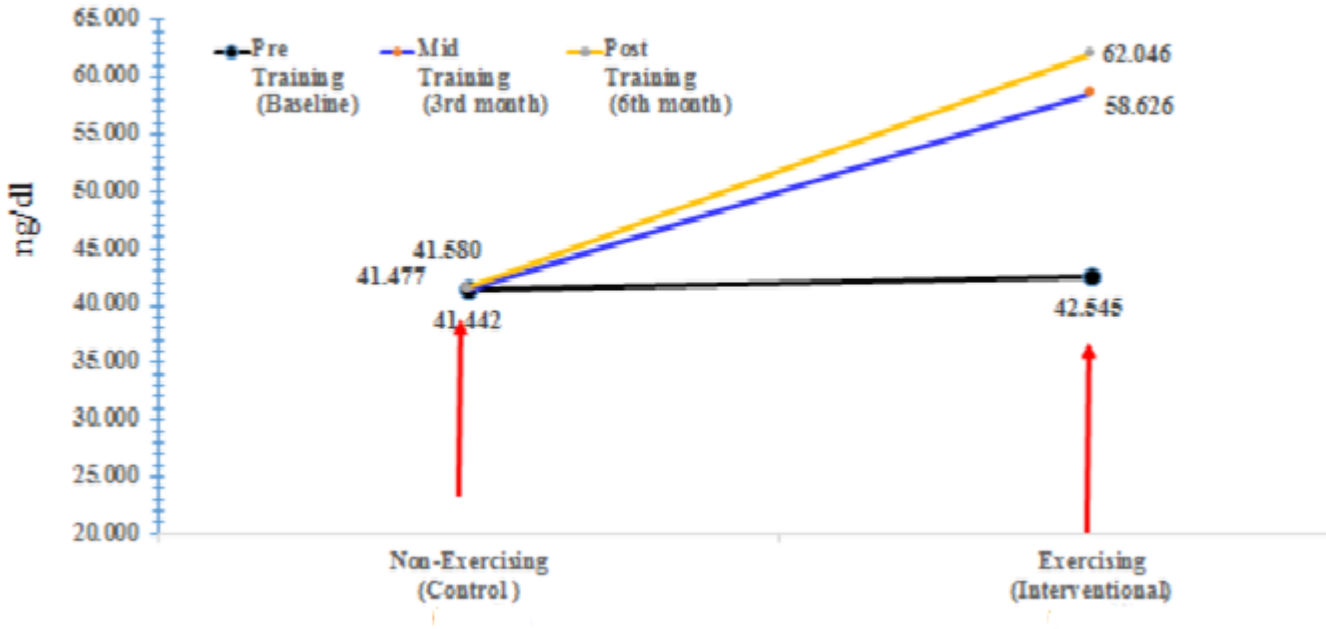

Figure 4.5. Comparison of procollagen type 1 N-terminal propeptide (P1NP) (ng/dl) in the control and intervention groups that did not exercise

In the group without osteoporosis, P1NP was significantly lower compared to normal and overweight subjects and compared to obese persons with osteoporosis. P1NP levels rose much faster in the intervention group, and BMD (T-Score) values in the intervention group only gradually improved.

Table 4.7. Correlation between P1NP and BMD (T-score) in Control (Non-Exercising Group)

P1NP	BMD (T-score)	Correlation (r)	P-value	Correlation interpretation
P1NP before training (ng/ml)	T- SCORE prior to training	0.13	0.058	• Very weak (0.00-0.19) • Weak (0.2-0.3) • Medium (0.4-0.5) • Strong (0.6-0.7) • Very strong (0.79-0.99)
P1NP before training (ng/ml)	T- SCORE between training	0.11	0.058	
P1NP before training (ng/ml)	T- SCORE after training	0.11	0.057	
P1NP between training (ng/ml)	T-SCORE pre training	0.10	0.051	
P1NP between training (ng/ml)	T-SCORE mid training	0.11	0.052	
P1NP between training (ng/ml)	T-SCORE post training	0.11	0.052	
P1NP after training (ng/ml)	T-SCORE pre training	0.10	0.051	
P1NP after training (ng/ml)	T-SCORE mid training	0.12	0.052	
P1NP after training (ng/ml)	T-SCORE post training	0.10	0.052	

*Significant ($p < 0.05$)

The results in table 4.7 depicts the correlations between the BMD and P1NP. P1NP had a significantly negative correlation with BMD.

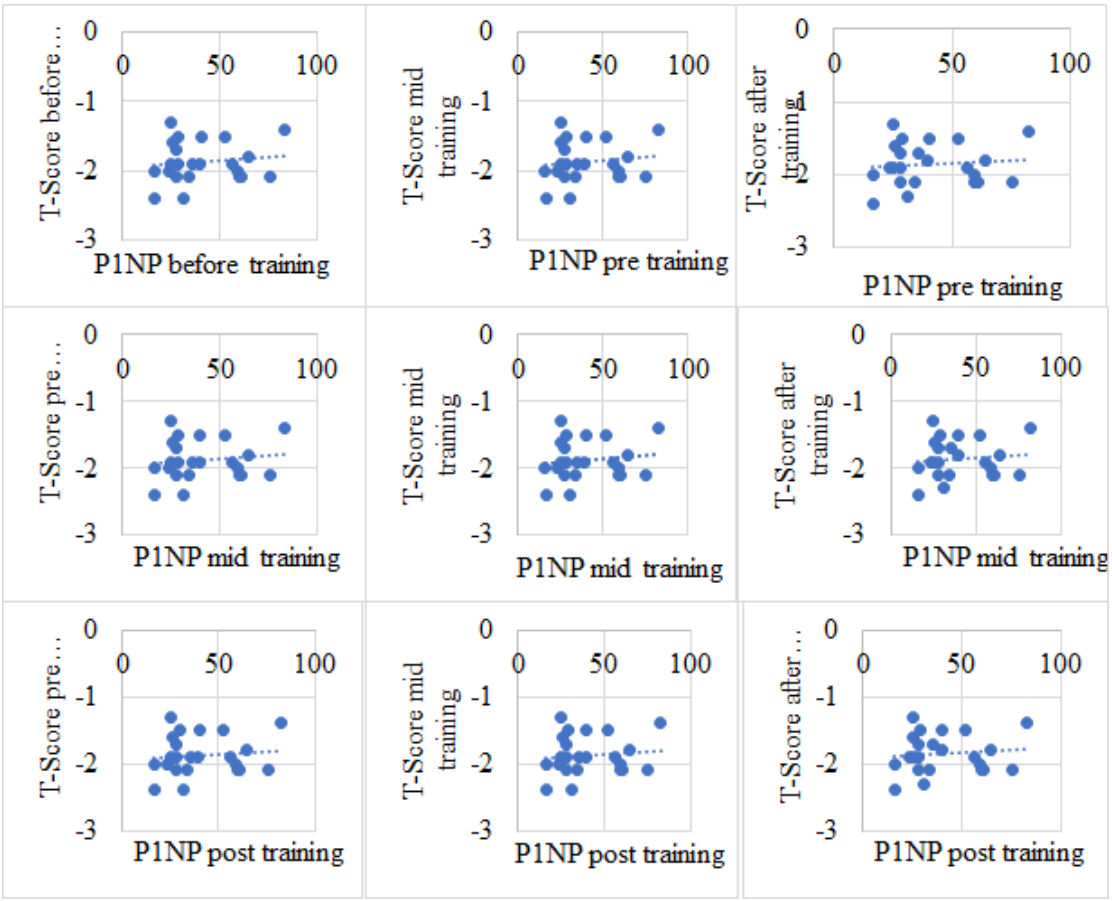

Figure 4.6. P1NP and BMD (T-score) Correlation in Control (Non-Exercising Group)

The relationships between bone turnover indicators and BMD at all sites in various populations are shown in Figure 4.6 using the cubic model. The value of bone resorption and formation biomarkers in the prediction of BMD was examined using logistic regression. P1NP was found to be a significant predictor of BMD in the univariate study.

Association between P1NP and BMD (T-score) in Interventional (Exercising Group)

Table 4.8. P1NP and BMD (T-score) Correlation in Interventional (Exercising Group)

P1NP	BMD (T-score)	Correlation (r)	P-value	Correlation interpretation
P1NP before training (ng/ml)	T- SCORE before training	0.90	0.052	• Very weak (0.00-0.19) • Weak (0.2-0.39) • Medium (0.40-0.599) • Strong (0.6-0.7) • Very strong (0.70-0.90)
P1NP before training (ng/ml)	T- SCORE between training	0.08	0.053	
P1NP pre training (ng/ml)	T- SCORE post training	-0.061	0.67	
P1NP mid training (ng/ml)	T- SCORE pre training	0.12	0.64	
P1NP mid training (ng/ml)	T- SCORE mid training	0.07	0.72	
P1NP mid training (ng/ml)	T- SCORE post training	-0.09	0.67	
P1NP post training (ng/ml)	T- SCORE pre training	0.1	0.6	
P1NP post training (ng/ml)	T- SCORE mid training	0.08	0.68	
P1NP post training (ng/ml)	T- SCORE post training	-0.06	0.69	

*Significant ($p < 0.05$)

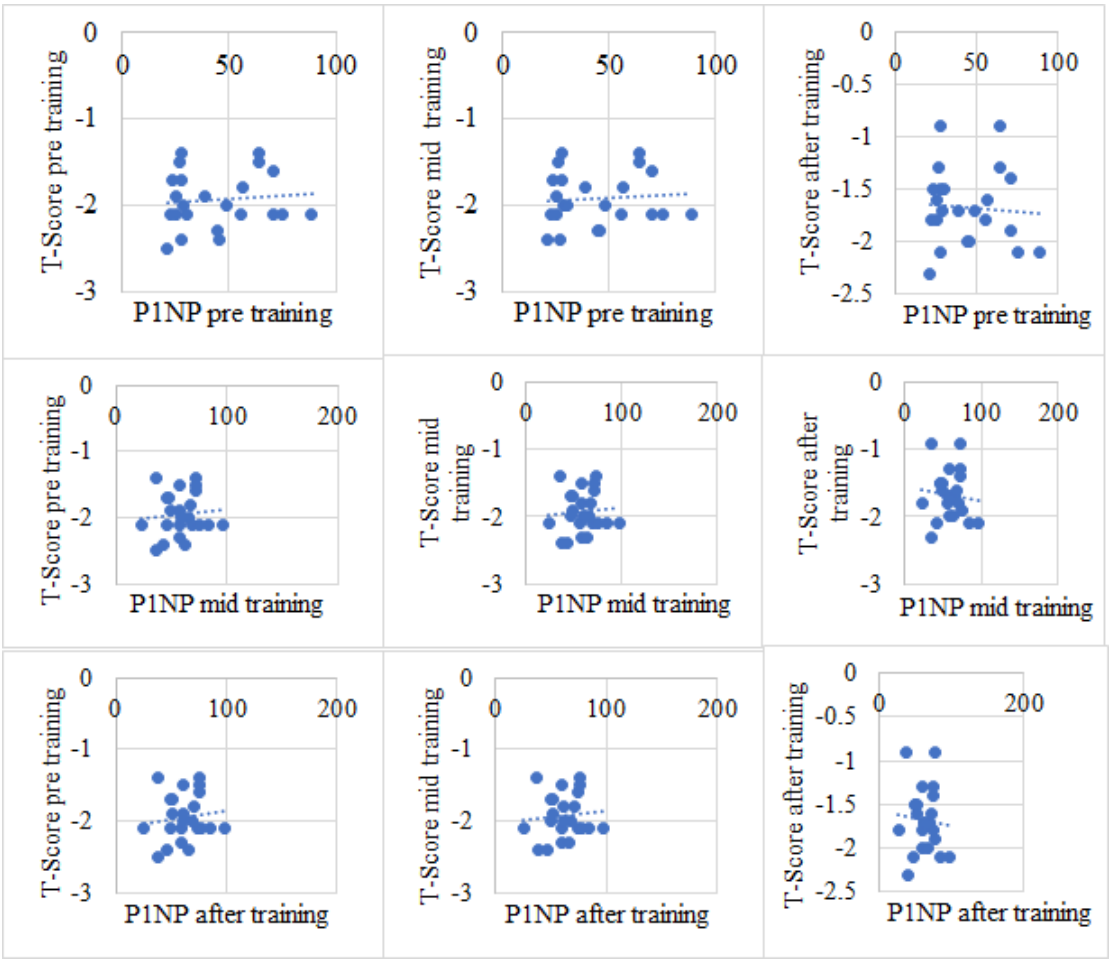

Figure 4.7. Correlation between P1NP and BMD (T-score) in Interventional (Exercising Group)

After puberty, bone synthesis stops, although bone remodelling by cells maintains a dynamic equilibrium between bone resorption and production. Regular exercise lowers the rate of bone loss and preserves bone tissue, reducing the likelihood of fractures.

Change in percentage in BMD and P1NP

Table 4.9. Percentage change results for PINP and BMD

P1NP	Number of Groups	before training	At Mid of training	difference	Percent Change	after training	Difference	Change in percent
P1NP (ng/ml)	Non-Exercising Group	41.442	41.477	0.035	0.08	41.580	0.138	0.33
	(Exercising Group)	41.5	55.6	15.9	35.8	59.7	17.5	42.8
BMD result	Non-Exercising Group	-1.8	-1.82	0.00	0.00	-1.80	0.03	0.80
	Exercising Group	-1.89	-1.89	0.02	0.90	-1.59	0.28	15.8

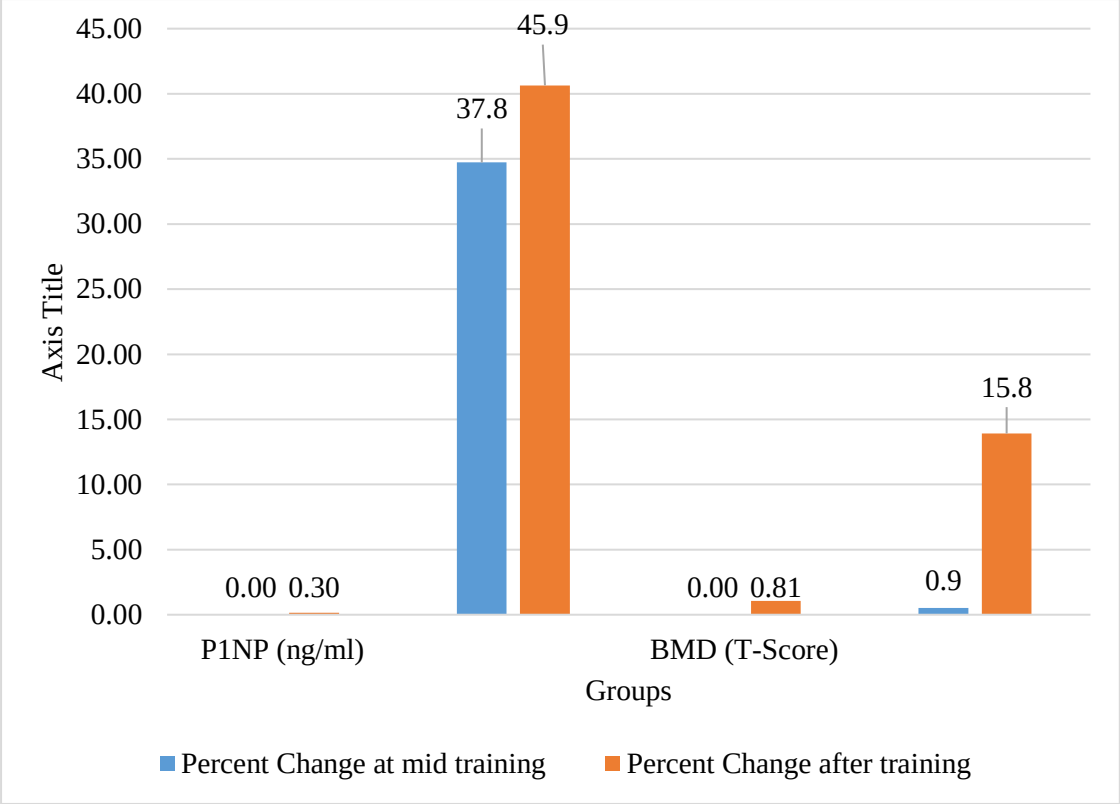

Figure 4.8. change in percentage in BMD and in P1NP

Conclusion

However, because it may take years or months to find changes in BMD, it lacks the benefit of early detection. Bone turnover markers (BTMs) can be easily and quickly detected in blood samples, and they may provide more sensitive information than BMD regarding changes in bone diseases. The kinetics of bone turnover in a variety of metabolic bone illnesses can be investigated using bone turnover indicators (BTMs). However, excessive bone turnover, such as that observed with ageing and pathological illnesses like osteoporosis, causes bone microarchitecture to degenerate when bone mineral density (BMD) is low, which raises the risk of fractures. By changing one's diet and lifestyle to include exercise, one can avoid having low bone mass. A sedentary lifestyle is detrimental to bone health. (Ooi & Sahrir, 2018) Exercise is crucial for the growth of bones. By putting mechanical strain on bones, exercise starts the metabolism of bones. Bone development is accelerated by mechanical tension. Exercise promotes bone growth in the following ways. Exercise

acts as a trigger to start the mechanical signal transduction process. Gap junctions allow the osteocytic network to transmit signals to the bone lining cells. By converting osteoprogenitors cells into osteoblasts, bone lining cells release paracrine substances such prostaglandins, growth hormones, and insulin. Accelerated bone loss was linked to higher pretreatment BTM levels. The relationship between BTMs and BMD is unfavourable. Procollagen type 1 N-terminal pro-peptide levels in the serum are lower, which indicates inadequate bone formation. A scheduled exercise programme was linked to an increase in serum P1NP and an improvement in bone densitometry. It is conceivable to use a technology that is more effective and economical for detecting therapy outcomes sooner in order to raise peak bone mass and avoid osteoporosis. In addition to improving quality of life, adverse effects can be avoided and time and money can be saved by choosing the administration of P1NP as an effective therapy.

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