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Serotonin Transporter Gene Polymorphisms and Bone Mineral Density in North Indian Postmenopausal Women

Kuzey Hindistan'daki Menopoz Sonrası Kadınlarda Serotonin Taşıyıcı Gen Polimorfizmlerinin Dolaşım Seviyesi ve Kemik Mineral Yoğunluğu ile İlişkisi

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Abstract

Objective: Osteoporosis is a serious metabolic bone disease worldwide, with genetic factors contributing significantly. We investigated the 5-HTT variable number tandem repeats (5HTTVNTR) & serotonin transporter gene 5-hydroxy tryptamine transporter linked polymorphic region or serotonin-transporter-linked promoter region (5HTTLPR) polymorphisms their serum levels & bone mineral density (BMD) in osteoporotic postmenopausal & healthy postmenopausal North Indian women.

Materials and Methods: In the present study, we included 165 post-menopausal osteoporotic (age 54.44±6.00) & 165 post-menopausal healthy North Indian women (age 54.47±6.46). BMD of different skeletal sites were analyzed using dual-energy X-ray absorptiometry. Serotonin serum level was assessed using enzyme linked immunosorbent assay & genotyping was done using polymerase chain reaction method.

Results: The current research demonstrated that in the patient group, subjects with the homozygous mutant 12/12 genotype of the 5HTTVNTR polymorphism exhibited significantly reduced BMD in the femoral neck region, accompanied by reduced serotonin levels. Similarly, subjects carrying the LL genotype of the 5HTTLPR variant showed significantly reduced BMD at both the lumbar spine & femoral neck, along with lower serotonin levels. In the controls, serum levels of both polymorphisms were found to be significantly lower. No significantly low BMD was found with homozygous mutant 12/12 genotype of 5HTTVNTR while LL genotype of 5HTTLPR showed significant decrease BMD at femoral neck. Furthermore, no significant variation was observed in serotonin genotype or allele frequencies among patients compared to controls.

Conclusion: This study indicates that serotonin gene polymorphisms may be linked with variations in BMD and involved in the development of osteoporosis in postmenopausal women from North India.

Keywords: Osteoporosis, serotonin transporter gene, postmenopausal women, BMD, genotype

Öz

Amaç: Osteoporoz, dünya çapında genetik faktörlerin önemli ölçüde katkıda bulunduğu ciddi bir metabolik kemik hastalığıdır. Menopoz sonrası osteoporotik ve menopoz sonrası sağlıklı Kuzey Hindistanlı kadınlarda 5-HTT değişken sayılı tandem tekrarları (5HTTVNTR) ve serotonin taşıyıcı geni 5-hidroksi triptamin taşıyıcı bağlantılı polimorfik bölge veya serotonin taşıyıcı bağlantılı promotör bölgesi (5HTTLPR) polimorfizmlerini, serum seviyelerini ve kemik mineral yoğunluğunu (KMY) araştırdık.

Gereç ve Yöntem: Bu çalışmaya 165 menopoz sonrası osteoporotik (yaş 54,44±6,00) ve 165 menopoz sonrası sağlıklı Kuzey Hindistanlı kadın (yaş 54,47±6,46) dahil edildi. Farklı iskelet bölgelerinin KMY'leri çift enerjili X-ışını absorpsiyometrisi ile ölçüldü. Serotonin serum seviyesi enzim bağlantılı immünosorbent testi ile değerlendirildi ve genotipleme polimeraz zincir reaksiyonu yöntemi kullanılarak yapıldı.

Bulgular: Bu çalışma, hasta grubunda, 5HTTVNTR polimorfizminin homozigot mutant 12/12 genotipine sahip deneklerin femur boynunda anlamlı derecede daha düşük KMY ve buna eşlik eden serotonin seviyelerinin azaldığını göstermiştir. Benzer şekilde, 5HTTLPR varyantının LL genotipine sahip deneklerde, hem lomber omurgada hem de femur boynunda anlamlı derecede düşük KMY ve daha düşük serotonin seviyeleri gözlenmiştir. Kontrol grubunda, her iki polimorfizmin serum seviyelerinin anlamlı derecede düşük olduğu bulunmuştur. Homozigot

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mutant 12/12 5HTTVNTR genotipinde anlamlı derecede düşük KMY bulunmazken, 5HTTLPR LL genotipinde femur boynunda anlamlı KMY düşüşü gözlenmiştir. Ayrıca, hastalar ve kontroller arasında serotonin genotipleri ve alellerinin sıklığında anlamlı bir fark gözlenmemiştir.

Sonuç: Bu bulgular, serotonin gen polimorfizmlerinin BMD'deki varyasyonlarla ilişkili olabileceğini ve Kuzey Hindistan'daki postmenopozal kadınlarda osteoporoz gelişimine katkıda bulunabileceğini düşündürmektedir.

Anahtar kelimeler: Osteoporoz, serotonin taşıyıcı gen, postmenopozal kadın, BMD, genotip

Introduction

Osteoporosis is a prevalent public health concern, defined by reduced bone strength and an elevated risk of fractures. Bone mineral density (BMD) and bone quality both play an important role in determining bone strength (1). BMD contributes to approximately 70% of the variability in bone strength, & findings from family and twin studies suggest that between 50% and 85% of BMD variability are influenced by genetic determinants (2-4). Since low BMD is a key contributor to the development of osteoporosis, it plays a critical role in disease prediction and prevention. Globally, osteoporosis affects an estimated 200 million women (5). In India about 50 million individuals were affected by either osteoporosis or osteopenia in 2013 (6).

Serotonin, referred as 5-hydroxytryptamine (5-HT), is a neurotransmitter whose transporter gene (*SLC6A4*) is approximately 31 kb in length, located on the 17p11.2 region of chromosome 17, and comprises 14 exons (7). It is expressed throughout various bone cell types, including osteoclasts, osteoblasts, osteocytes, and osteoblast precursor cells, & is considered to play a significant role in regulating bone mass formation. Two polymorphic regions have been observed in the *SLC6A4* gene. The first referred to as 5-HTT variable number tandem repeats (5-HTTVNTR), is situated in intron 2 and consists of a variable number of tandem repeats (VNTR), with alleles carrying 9, 10, or 12 copies of a 17-base pair sequence. The second polymorphism is a 44 bp insertion/deletion (indel) polymorphism situated in the promoter region, known as 5-hydroxy tryptamine transporter linked polymorphic region or serotonin-transporter-linked promoter region (5HTTLPR), which results in two alleles: the short (S) allele containing 14 repeats & the long (L) allele carrying 16 repeats (8-11).

Recent advances in bone biology have revealed a role for the serotonergic system traditionally studied in the context of neuropsychiatric function in the regulation of bone homeostasis in peripheral tissues. Ferreira et al. (12), 2011 demonstrated that the 5-HTTVNTR polymorphism has been significantly linked with an increased risk of osteoporosis. Previous studies have revealed that the long (L) allele results in normal transcription, whereas the short (S) variant is less effective (13-15). Additionally, some studies have found that the S allele of 5-HTTLPR is significantly associated with decreased BMD, while the L allele shows no such association (16,17).

Several studies have been conducted on serotonin gene polymorphism, but a comprehensive study on the effect of serotonin gene polymorphism on BMD and serotonin levels has not been done in this ethnic group so in a current study, we have explored the association between serotonin transporter gene (*5HTTVNTR* & *5HTTLPR*) polymorphisms with their circulatory levels & BMD in North Indian postmenopausal women.

Materials and Methods

Subjects

In this case control study we enrolled 165 postmenopausal osteoporotic women (patients) (mean age 54.44±6.00) and 165 postmenopausal healthy women (controls) (mean age 54.47±6.46) who visited OPD at the Department of Orthopedics, King George Medical University, Lucknow, India between December 2018 and April 2021. For at least one year, all the women did not experienced menstruation. Before participating in this study, we obtained a questionnaire from each participant's current health status and medical history with informed consent. The study received ethical approval from the Institutional Ethics Committee of King George's Medical University, Lucknow, India (approval number: 1094, dated: 29.07.2019). Dual-energy X-ray absorptiometry (DEXA) was used for the assessment of each individual's BMD at different skeletal sites. According to the World Health Organization (WHO) criteria of osteoporosis, the individuals were categorized as osteoporotic or normal based on the T-score of DEXA, and after that sample was taken from all recruited subjects.

BMD Measurements

At the skeletal site of the hip, forearm, femoral neck & lumbar spine L1-L4, the BMD (g/cm^2) was evaluated by DEXA. The range of variance percent coefficient was 0.5% to 1.1% based on the measurement site. The peak bone density (T-score) of a healthy young adult of the same sex is defined by the WHO as BMD values at or above -1 standard deviation (S.D.). Osteoporotic BMD was defined as a measurement at or below -2.5 S.D.

DNA Isolation and Genotyping

For serotonin transporter gene genotyping, 5 mL of venous blood was collected from each subject. Of this, 2 mL was collected into ethylene diamine tetra acetic acid vials for DNA isolation using the salting-out method, to study genetic polymorphisms. The serum was extracted from 3 mL of blood collected in the plain vial by centrifuging at 3000 rpm for 5 minutes. The resulting serum was then stored at -20 °C for enzyme linked immunosorbent assay analysis. The extracted DNA was utilized to genotype *5-HTTVNTR* and *5-HTTLPR* gene polymorphisms using the polymerase chain reaction (PCR) method. Both polymorphisms produced distinct amplicons, as identified through 3% agarose gel electrophoresis.

Detection of Serotonin Transporter Gene 5HTTVNTR Polymorphism

PCR was conducted to identify the 5-HTTVNTR polymorphism in the serotonin transporter gene, using the primers F-5′ GTCAGTATCACAGGCTGCGAG 3′ and R-5′ TGTTCCTA GTCTTACGCCAGTG 3′. The PCR reaction mixture was prepared in a final volume of 25 µL containing 2x PCR master mix, 150-200 ng genomic DNA, 10pmol of each primer (forward & reverse). PCR amplification was performed for 5 min at 94 °C followed by 30 cycles of 94 °C/40 sec, 57 °C/40 sec, extension at 72 °C/40 sec & final extension for 5 minutes at 72 °C. All the PCR reactions were performed using an automated thermal cycler (BIO-RAD T100). In 5-HTTVNTR polymorphism PCR product was separated by 3% agarose gel electrophoresis containing ethidium bromide to enable the detection of 267 bp (10/10), 267 bp, 299 bp (10/12) and 299 bp (12/12) genotypes.

Detection of Serotonin Transporter Gene 5HTTLPR Polymorphism

PCR was conducted to identify the 5-HTTLPR polymorphism in the serotonin transporter gene, using the primers F-5′-ATGCCAGCACCTAACCCCTAATGT-3′ & R-5′-GGACCGCAA GGTGGGCGGGA-3′. The PCR reaction mixture was prepared in a final volume of 25 µL containing 2x PCR master mix, 150-200ng genomic DNA, 10 pmol of each primer (forward & reverse). PCR amplification was performed for 5 min at 95 °C followed by 35 cycles of 95 °C/30 sec, 66 °C/40 sec, extension at 72 °C/40 sec & final extension for 5 minutes at 72 °C. All the PCR reaction were performed using an automated thermal cycler (BIO-RAD T100). In 5-HTTLPR polymorphism PCR product was separated by 3% agarose gel electrophoresis containing ethidium bromide to enable the detection of 375 bp (S/S), 375 bp, 419 bp (S/L) and 419 bp (L/L) genotypes.

Statistical Analysis

The statistical analysis was conducted using INSTAT version 3.05 (Graph Pad Software, San Diego, CA, USA). All categorical variables were summarized as percentages. The study had a statistical power of 90%, determined from the odds ratio (OR) of the study genotype under both the null and research hypotheses. Numerical data were expressed as mean values with S.Ds. Genotype frequencies were consistent with Hardy-Weinberg equilibrium. Comparisons of genotype & allele distributions between patients & controls were performed using the chi-square test. The independent samples t-test was employed to compare mean values between the case & control groups, while One-Way ANOVA was comparisons involving more than two groups. Adjusted ORs with 95% confidence intervals were used to analyze the associations of genetic, demographic, and anthropometric factors with the osteoporosis. Logistic regression analysis was used to calculate adjusted OR and 95% confidence interval for the genotypes. Adjustments were made for age, body mass index (BMI), and years since menopause. A p-value of ≤0.05 was considered statistically significant.

Results

The baseline characteristics of the patients & controls are presented in Table 1. BMD across various skeletal regions was found to be significantly low in the patients in comparison to the controls (p≤0.0001**). Height is also significantly decreased in patients as controls (p=0.035*). Additionally, BMI & serum serotonin levels were significantly higher among patients than among controls (p=0.046*; p<0.0001*).

Figure 1 illustrates the comparison of BMD across different skeletal sites & serotonin levels among patients, categorized by the various genotypes of 5HTTVNTR and 5HTTLPR. The present investigation revealed that individuals carrying the homozygous mutant 12/12 genotype of 5HTTVNTR had significantly reduced BMD at the femoral neck, along with lower serotonin levels, compared to those with the 10/10 and 10/12 genotypes. Additionally, for 5HTTLPR, individuals with the homozygous mutant LL genotype exhibited significantly reduced BMD at the

Table 1. Biochemical and anthropometric characteristics of patients and controls

S.no.	Variables	Postmenopausal women with osteoporosis (n=165)	Postmenopausal women without osteoporosis (n=165)	p-value
1.	Age	54.44±6.00	54.47±6.46	0.959
2.	Weight	57.67±10.06	56.78±7.03	0.355
3.	Height	152.07±6.48	153.64±6.98	0.035*
4	BMI	24.86±3.98	24.07±3.02	0.046*
5.	YSM	9.33±5.92	9.53±6.50	0.770
6.	BMD L_1-L_4 lumbar spine (g/cm^2)	0.69±0.12	0.89±0.12	<0.0001**
7.	BMD hip (g/cm^2)	0.54±0.13	0.84±0.11	<0.0001**
8.	BMD forearm (g/cm^2)	0.58±0.13	0.81±0.11	<0.0001**
9.	BMD femoral neck (g/cm^2)	0.66±0.11	0.78±0.09	<0.0001**
10.	Serotonin (ng/mL)	103.80±19.96	122.10±36.51	<0.0001*

All data are shown as mean ± standard deviation, p<0.05 is considered statistically significant, BMI: Body mass index, YSM: Year since menopause, BMD: Bone mineral density, kg: Kilogram, cm: Centimetre, kg/m^2: Kilogram per square metre, kg: Kilogram, g/cm^2: Gram per square centimetre, ng/mL: Nanograms per millilitre

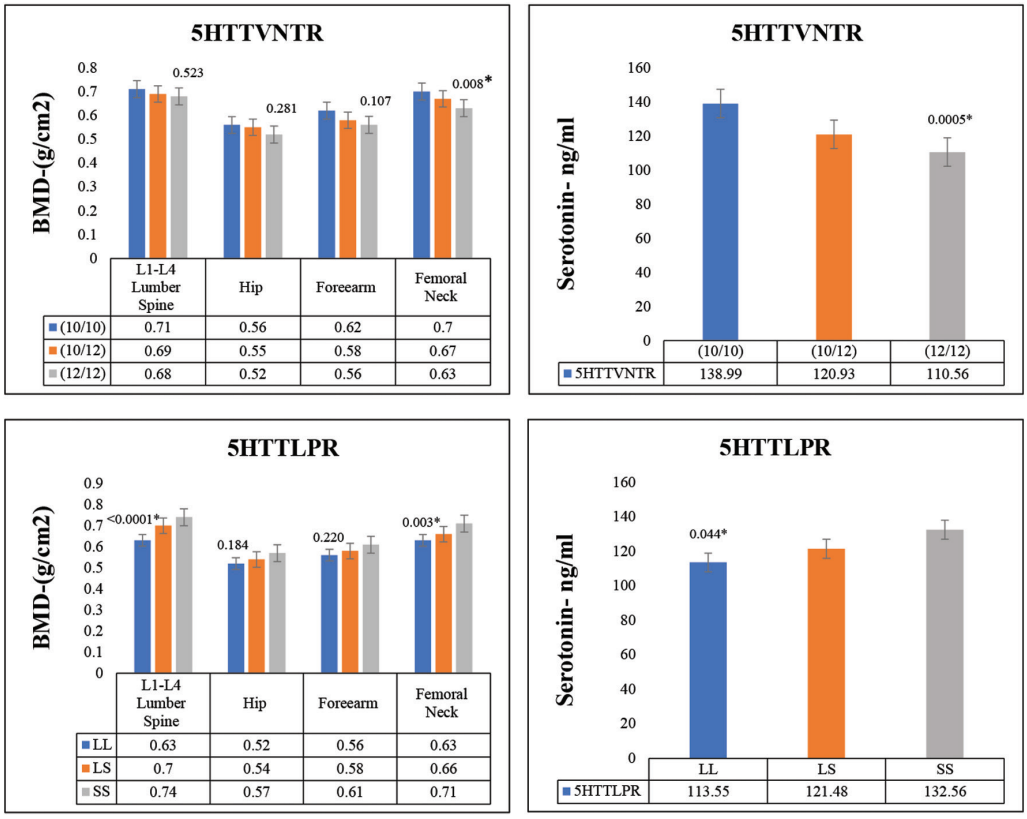

Figure 1. The comparison of BMD at different skeletal sites and serotonin among patients according to different genotypes of serotonin – *5HTTVNTR* and *5HTTLPR* gene polymorphism
BMD: Bone mineral density, 5HTTVNTR: 5-HTT variable number tandem repeats, 5HTTLPR: 5-hydroxy tryptamine transporter linked polymorphic region or serotonin-transporter-linked promoter region

femoral neck & lumbar spine along with lower serotonin levels, in comparison to those with the LS and SS genotypes.

Figure 2 illustrates the comparison of BMD at various skeletal locations & serotonin levels in the control group, categorized by different genotypes of 5HTTVNTR and 5HTTLPR. Current study revealed that participants carrying homozygous mutant 12/12 genotype of 5HTTVNTR showed low BMD at various skeletal locations & low serotonin level as compared to 10/10 & 10/12 genotypes. For 5HTTLPR, individuals with the homozygous mutant LL genotype exhibited decreased BMD at various skeletal regions & significantly reduced BMD at the femoral neck along with low serotonin levels, in comparison to those with the LS and SS genotypes.

A comparison of frequency distribution of serotonin genotypes & alleles (5HTTVNTR and 5HTTLPR) between the patient & control groups, followed by univariate analysis is illustrated in Table 2. In case of 5HTTVNTR, the genotype frequencies of 10/10, 10/12 and 12/12 in patients were 25.45%, 41.21% and 33.33% as compared to 27.27%, 43.64% and 29.10% in controls, respectively. The difference between the groups was not statistically significant (p=0.707). Similarly, the distribution of the 10 and 12 alleles at 5HTTVNTR did not differ significantly between patients and controls (p=0.483). For 5HTTLPR, the genotype frequencies of the LL, LS, and SS genotypes among patient group were 29.10%, 44.85%, and 26.10%, compared to the frequencies 26.10%, 49.10%, and 24.85 in controls. No statistically significant difference was observed in the genotype distribution between patients & controls (p=0.727). Additionally, the allele frequencies (L and S) at 5HTTLPR also showed no significant difference between patients and controls (p=0.876). The genotype frequency distribution among both groups (patients & controls) adhered to Hardy-Weinberg equilibrium. For 5HTTVNTR, the p-values were 0.06 in patient group & 0.10 in control group, while for 5HTTLPR; the p-values were 0.08 in patient group & 0.60 in control group.

Logistic regression analysis for 5HTTVNTR and 5HTTLPR indicated that there were no significant distinctions between the patient & controls, as presented in Tables 3 and 4.

Discussion

A neuropeptide serotonin (5-hydroxytryptamine, 5-HT) has attracted significant interest in recent years because of its possible involvement in bone metabolism (18,19). The serotonin gene polymorphisms have been widely studied across various populations. Current study demonstrated that participants with homozygous mutant 12/12 genotype of 5HTTVNTR & LL genotypes of 5HTTLPR exhibited low BMD at various skeletal

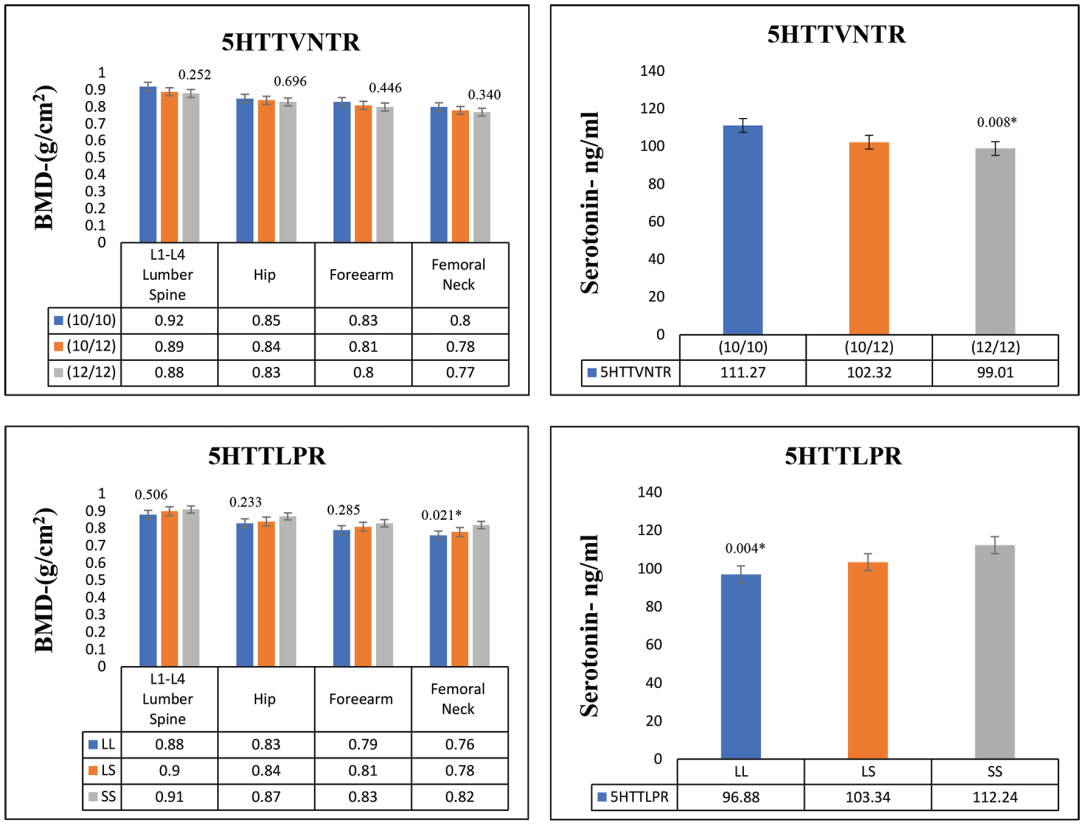

Figure 2. The comparison of BMD at different skeletal sites and serotonin among controls according to different genotypes of serotonin – *5HTTVNTR* and *5HTTLPR* gene polymorphism
BMD: Bone mineral density, 5HTTVNTR: 5-HTT variable number tandem repeats, 5HTTLPR: 5-hydroxy tryptamine transporter linked polymorphic region or serotonin-transporter-linked promoter region

Table 2. Frequency distribution of genotypes and alleles of 5HTTVNTR and 5HTTLPR among patients and healthy controls by univariate analysis

	5HTTVNTR		
Genotypes	**Patients (165)**	**Controls (165)**	**p-value**
10/10 10/12 12/12	42 (25.45%) 68 (41.21%) 55 (33.33%)	45 (27.27%) 72 (43.64%) 48 (29.10%)	0.707
Alleles			
10 12	152 (46.10%) 178 (53.94%)	162 (49.10%) 168 (50.90%)	0.483
5HTTLPR			
Genotypes	**Patients (165)**	**Controls (165)**	**p-value**
LL SL SS	48 (29.10%) 74 (44.85%) 43 (26.10%)	43 (26.10%) 81 (49.10%) 41 (24.85%)	0.727
Alleles			
L S	170 (51.52%) 160 (48.48%)	167 (50.61%) 163 (49.39%)	0.876

p<0.05 is considered statistically significant, data is presented in number and percentage, 5HTTVNTR: 5-HTT variable number tandem repeats, 5HTTLPR: 5-hydroxy tryptamine transporter linked polymorphic region or serotonin-transporter-linked promoter region

sites along with lower serotonin levels. Study by Gustafsson et al. (20), says that serotonin stimulated osteoblasts to secrete more osteoprotegerin while reducing the release of receptor activator of NF-κB ligand, indicating its involvement in osteoblast-driven suppression of osteoclast differentiation. Administering serotonin led to a notable increase in BMD suggesting that serotonin positively influences bone formation in rat (20). The research carried out by Wang et al. (21) in postmenopausal women showed that lower serum serotonin level is associated with reduced BMD of femoral neck which is consistent with our findings. Moreover Wei et al. (22), 2017 demonstrated that low serum serotonin levels are linked with low BMD at lumbar spine & femoral neck in postmenopausal women which implies its positive correlation with BMD.

Mödder et al. (23), 2010 observed a tendency for an inverse correlation with serum serotonin levels & lumbar spine BMD in postmenopausal women. As presented Kim et al. (24) investigation that elevated serum serotonin levels were linked specifically to reduce BMD in the lumbar spine. Zhang and Drake (25) reported that higher level of 5-HTT is also linked with lower BMD which is responsible for reduced bone formation activity. The S allele was linked to a greater risk of decreased BMD in the lumbar spine & radial sites (26). Our observation is contradictory with above findings.

Table 3. Comparison of frequency distribution of 5HTTVNTR genotypes among patients and controls after adjusting for age, YSM & BMI

	5HTTVNTR				
Genotype	**Patients (n=165)**	**Control (n=165)**	**p**	**OR**	**95% CI**
Codominant model					
10/10	42 (25.45%)	45 (27.27%)	Ref.	Ref.	Ref.
10/12	68 (41.21%)	72 (43.64%)	0.965	1.012	(0.592-1.729)
12/12	55 (33.33%)	48 (29.10%)	0.482	1.228	(0.693-2.174)
Dominant model					
10/10	42 (25.45%)	45 (27.27%)	Ref.	Ref.	Ref.
10/12+12/12	123 (74.55%)	120 (72.73%)	0.708	1.098	(0.673-1.793)
Recessive model					
10/10 +10/12	110 (66.67%)	117 (70.91%)	Ref.	Ref.	Ref.
12/12	55 (33.33%)	48 (29.10%)	0.265	1.302	(0.818-2.071)

p<0.05 is considered statistically significant, data is expressed in number and percentage, 5HTTVNTR: 5-HTT variable number tandem repeats, BMI: Body mass index, YSM: Year since menopause, OR: Odds ratio, CI: Confidence interval

Table 4. Comparison of frequency distribution of 5HTTLPR genotypes among patients and controls after adjusting for age, YSM & BMI

	5HTTLPR				
Genotype	**Patients (n=165)**	**Controls (n=165)**	**p**	**OR**	**95% CI**
Codominant model					
LL	48 (29.10%)	43 (26.10%)	Ref.	Ref.	Ref.
SL	74 (44.85%)	81 (49.10%)	1.551	0.818	(0.487-1.374)
SS	43 (26.10%)	41 (24.85%)	1.163	0.940	(0.519-1.701)
Dominant model					
LL	48 (29.10%)	43 (26.10%)	Ref.	Ref.	Ref.
SL+ SS	117 (70.91%)	122 (73.94%)	1.462	0.859	(0.530-1.393)
Recessive model					
LL+ SL	122 (73.94%)	124 (75.15%)	Ref.	Ref.	Ref.
SS	43 (26.10%)	41 (24.85%)	0.800	1.066	(0.649-1.750)

p<0.05 is considered statistically significant, data is expressed in number and percentage, 5HTTLPR: 5-hydroxy tryptamine transporter linked polymorphic region or serotonin-transporter-linked promoter region, BMI: Body mass index, YSM: Year since menopause, OR: Odds ratio, CI: Confidence interval

According to Ferreira et al. (12) the genotypic frequencies of 10/12 and 12/12 were higher in patients then in controls which are in concordance with our results. Reduced bone formation has been linked to the L allele of the low-expressing serotonin receptor (HTR1B) (26).

This is, to our knowledge, the first evidence in postmenopausal North Indian women demonstrating a significant link with serotonin transporter polymorphisms (5HTTVNTR & 5HTTLPR), their circulating serotonin levels, and BMD which providing a multiple aspect understanding of the potential genetic and molecular mechanisms underlying osteoporosis. It will also help us better understand the onset and progression of this disease.

Study Limitations

There are certain limitations to our study that should be acknowledged, all subjects were enrolled from a single medical center within the same geographic region, & the results may not be fully generalizable to the wider Indian population due to differences in environmental conditions across regions. Second, the relatively small sample size may have influenced the results, and the observed effects may differ from those in larger and more diverse group.

Future Direction

This regionally focused investigation provides a methodological and conceptual framework for future multicentric and large-scale genetic studies on osteoporosis in diverse Indian populations. A prospective longitudinal design should be used to better clarify the causal relationship between 5HTTVNTR & 5HTTLPR genotypes, serum serotonin levels, and variations in BMD over time. Future studies should also systematically control for possible confounding variables, like lifestyle parameters, dietary pattern, comorbid conditions, and the use of medications, which can affect both serotonin levels and bone metabolism. Collectively, these measures will enhance mechanistic understanding and facilitate the development of targeted preventive and therapeutic interventions for postmenopausal osteoporosis.

Conclusion

We conclude that homozygous mutant genotype 12/12 of 5HTTVNTR and LL of 5HTTLPR lower serum serotonin levels thereby reducing BMD at hip, forearm, femoral neck & Lumbar spine in North Indian postmenopausal female.

A more detailed investigation of genetic factors will enhance our insight of the underlying of osteoporosis pathogenesis, as well as the inter-individual variability observed in its onset and progression. In clinical practice, identifying and mapping genes that influence BMD could lead to the discovery of novel molecular pathways for developing treatments in bone-related disorders. Although the contribution of individual genetic variants may be modest, their associated signaling pathways are likely to play a significant role in metabolic processes of bone. Consequently, these pathways represent promising targets for the creation of new pharmaceutical interventions aimed at the prevention and therapy of osteoporosis and other skeletal diseases. Furthermore, advances in osteoporosis genetics may also contribute to the establishment of improved diagnostic and predictive approaches for assessing individual disease risk.

Ethics

Ethics Committee Approval: The study received ethical approval from the Institutional Ethics Committee of King George's Medical University, Lucknow, India (approval number: 1094, dated: 29.07.2019).

Informed Consent: Before participating in this study, we obtained a questionnaire from each participant's current health status and medical history with informed consent.

Footnotes

Authorship Contributions

Concept: P.D., I.A., S.W., T.J., Design: P.D., I.A., S.W., T.J., Data Collection or Processing: P.D., I.A., S.W., T.J., Writing: P.D., I.A., S.W., T.J.

Conflict of Interest: No conflict of interest was declared by the authors.

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