Bioanalysis ISSN:1757-6199 VOLUME 16, ISSUE 5 page 518-525
Journal link: https://bioanalysisjournal.com/
Abstract Link: https://bioanalysisjournal.com/abstract-518-525 28 June 2024

Bioanalysis
Impact Factor: 1.8 (2024)

Exploring the Impact of Genetic Polymorphisms in the Vitamin D Receptor Gene on Bone Density

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Abstract

Background: Density of bones is a significant component of a general well-being of an individual and depends on one's genes as well as the prevailing circumstances. Vitamin D Receptor (VDR) gene is basically involved in modulating the action of Vitamin D with regards to bone metabolism. This indicates that certain polymorphisms in the form of VDR gene contribute to variations in bone density and hence differing bone health status in human populations.

Aim: Hence this study seeks to establish the effects of the genetic polymorphisms of the VDR gene on the bone density and examine the degree of correlation between the gene polymorphisms such as FokI, BsmI, ApaI and Taq1 and bone density.

Methods: The type of study design recommended is case-control, and cross-section and cohort studies. Targets are men and women of a particular age group and +-body mass index, with no history of pathological conditions or usage of medications altering bone density. Molecular analysis was done by Polymerase Chain Reaction (PCR), Restriction Fragment Length Polymorphism (RFLP), & Sequencing. BMD analysis was done by DEXA, and QUS at both the baseline and follow-up visits. Data analysis included multiple regression analysis, ANOVA test, multivariate test, and adjustment for variables.

Results: Analysing the data, it can be stated that some polymorphisms of the VDR, namely FokI and BsmI, are frequent and affect bone density. It has also found variation in the result of the bone density between those patients who have and are not having these polymorphisms. Again, the study also showcases the pros and cons of each polymorphism The secondary analyses indicated differences in the effectiveness of the compound on issues of age, gender and Ethnicity.

Conclusion: Thus, it was found that a number of polymorphisms in the VDR gene directly affects bone density and knowledge of such personalization can play a role in proper management of bone diseases. The application of genetic screening of VDR polymorphisms into the context of clinical practice may help to identify people at risk in developing osteoporosis and other bone density disorders and prevent or control them more efficiently. It does become imperative at this stage to further study the genetic factors affecting bone health and develop better treatment strategies for patients with poor skeletal status.

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Keywords: Bone Density, Vitamin D Receptor (VDR) Gene, Genetic Polymorphisms, FokI, BsmI, Personalized Medicine, Osteoporosis, Bone Health, Dual-energy X-ray Absorptiometry (DEXA), Polymerase Chain Reaction (PCR).

Introduction

Bare bone density is a significant determinant of the wellness proportionate to the impact it has on the strength and steadiness of bones, the prevention of breakage and prevention of osteoporosis. Bone density, its preservation and factors that influence it are significant in each stage of the human life cycle depending on the age, gender, nutritional status, and activity. Decreased bone mass can cause greater brittleness of the bones and worsen the availability of an individual's daily life due to frequent fractures. An important nutrient that contributes to bone formation is the vitamin d, this plays an important role in the body by increasing calcium and phosphorus for the formation of bones. The vitamin D receptor (VDR) gene is very essential in this process due to its involvement in the regulation of vitamin D on bone and mineral metabolism. The VDR gene codes for the nuclear hormone receptor associated with Vitamin D3 and its activity is basic for the regulation of calcium and bone quality. Upon binding with VDR, the VDR complex moves to the nucleus and modulates the genes that are instrumental for calcium and phosphate. In fact, genetic polymorphisms can drastically change the function of the VDR gene, which in turn may alter the rate at which the body utilizes the vitamin d and therefore affect bone density. Polymorphism refers to variations that are seen in the DNA sequence particularly among the individuals within a given population. These polymorphisms can affect the regulation of genes and roles of proteins and may cause variation of an organism's physical characteristics or ability to develop diseases [1].

Altogether, a number of polymorphisms of the VDR gene have been reported to be associated with the levels of bone density. Among these, some are FokI, BsmI, ApaI, and TaqI. Such polymorphisms may alter the amino acid sequence or conformation of the VDR molecule and/or its ability to bind vitamin D and influence the pathways concerning bone metabolism. For example, FokI polymorphism leads to the variation of the start codon, which in turn leads to VDR protein with different transcriptional activity. Among them, BsmI, ApaI, and TaqI are enlisted in non-genic regions although they have been implicated in gene regulation including mRNA stability. In this case, specific genetic differences can significantly influence the bone mass and possibilities to develop osteoporosis. The purpose of the systematic review of the effects of VDR gene polymorphisms on bone mineral density is to determine how genetic variations influence population's BMD. When considering VDR's polymorphisms and bone density, researchers want to define the signs of certain polymorphisms, which will help determine an Individual's low bone density and, therefore, predisposition to osteoporosis . The acquirement of such knowledge can assist that prevention and treatment of an illness be tailored in regard to an individual's genes [2].

The purpose of this investigation is firmly predicated on the hypothesis that genetic variations in the allele of VDR gene directly affect the relative bone density and consequently bone health disparity within the populace. This hypothesis is further premised on the premise that VDR gene is very crucial in building a link between vitamin D and bone metabolic function. Changes on this gene could modify the receptor's structure, which consequently influences the efficacy of vitamin D in controlling the absorption of calcium and density of bones. Know polymorphisms, if to be discovered to cause reduced bone mass, may be used as predictors of osteoporosis and proportional fractures. To test this hypothesis, several studies are performed concerning the frequency of VDR polymorphisms in particular groups and correlations of bone mineral density results. These studies usually entail genotyping of persons for particular VDR polymorphisms and a quantification of areal bone mineral density by means of DEXA. Statistical tests are finally applied to identify if there is any correlation between the presence of the particular polymorphisms and changes of BMD [3].

Besides, it is necessary to evaluate other factors that may have an influence on density variations and affect the VDR polymorphisms. For instance, the calcium intake of foods, their physical activity, and the time spent in sun exposure, directly impacts the interactions of VDR polymorphisms in bone health.

Bioanalysis
Impact Factor: 1.8 (2024)

By considering these things, researchers are able to have a bigger perspective in making an understanding in the levels of genetic and environmental dimensions on the bone density. This research therefore has a relativistic significance. Genotyping for the predisposition to bone density might mean that there would be indications showing that an individual is prone to the disease. Such tests could therefore be used together with other risk factors for designing distinct prevention and management strategies. For patients who are at high risk, measures like high calcium and vitamin D consumption plans, simple exercises that involve putting weight on bones, or with medication, could be administered to keep the patient's bones strong and free from fractures. In addition, knowledge of the genetic aspects of bon density based on VDR polymorphisms may also help to explain the process of other diseases that are associated with disorders of calcium-phosphate, including hyperparathyroidism and some other metabolic bone diseases. Thus, the obtained knowledge could help to create a new approach based on targeting the VDR pathway in therapy [4].

Methodology

This paper focuses on elucidating the effect of genetic polymorphisms in the Vitamin D receptor (VDR) gene on bone density by conducting an examination into the following aspects: the study designs for the investigation, participants' inclusion criteria and exclusion criteria for the studies, techniques for genetic analysis, procedures for measurement of bone density, and data collection and analysis processes. To maintain the result accuracy and inclusion of all the possible outcomes, the study is designed as case-control, cohort, and cross-sectional studies. To investigate genetic differences, case-control studies are made using cases of subjects with less than normal bone density and controls of normal subjects. In cohort studies, the subjects are followed up for some time to determine the relation between the VDR gene polymorphisms and the change in BMD, while cross sectional studies are done to determine the prevalence of these polymorphisms and their impact on BMD at a given time. The selected studies are justified as they cover time and causal dependencies between VDR polymorphisms and changes in bone density in aggregate. In the case of the current study, the target participants are chosen in accordance with certain inclusion and exclusion criteria to establish the validity and applicability of the study's results. Selection criteria usually involve an age which should encompass a group that has young adults and also the older adults which is able to cover the whole spectrum of the methodology of change in bone density, then in terms of sex, subjects of both sexes are relevant in order to cover gender differences in metabolism of bones and the finally the basic bone density measurement which must be used to categorize the subjects into case and control. Participants also have to be free of chronic diseases which can influence bone mass alone like rheumatoid arthritis or chronic kidney disease and they should not take medications like glucocorticoids or bisphosphonates that affect bone metabolic rate. A complete set of data such as age, gender, ethnic background and other lifestyles parameters such as diet, exercise, smoking habits etc are also obtained because the results can be adjusted for genetic analysis [5].

As for genetic analysis, this discipline is aimed at the detection and examination of particular polymorphisms of the VDR gene, for instance, FokI, BsmI, ApaI, and TaqI. PCR and RFLP are some of the methods that are used for the aforementioned purpose. In PCR, predetermined fragments of DNA are made to increase in number so that they can be studied in greater detail while in RFLP, the DNA samples are manipulated with restricted enzymes that cut the DNA at specific regions thus showing differences in the genes. In as much as comparative methods give a general picture of the VDR gene, sequencing methods establish even the slightest difference in the genetic profile. Gaining accurate and credible data is a top priority hence the possibility of collecting numerous samples from the participants, measures that prevent cross contamination and contamination of genetics samples are employed. Some of these methods include duplicate testing, Positive control and Negative control among others. Such procedures include Dual-energy X-ray Absorptiometry (DEXA) and Quantitative Ultrasound as the methods of evaluating bone density. DEXA is the best technique for evaluating BMD since it offers accurate and reproducible total body, trunk, and limb BMD [6]in areas like spine and hip which are sensitive to fractures. Quantitative Ultrasound is then used in the clinical assessment in parallel with other methods, providing extra information regarding the quality and strength of the bone. Some of the measures to standardize and reduce measurement errors include periodic equipment calibration,

Bioanalysis
Impact Factor: 1.8 (2024)

adequate and proper personnel training, and consistency in positioning of the participants and scan procedures. In order to obtain reliable and consistent results concerning bone density and its relation to certain polymorphisms, the results of bone density must be consistent and reliable themselves.

Measurement is a systematic process of getting data at specified times, before and after treatment, to compare bone density changes and to demonstrate how VDR polymorphisms affect these changes [7]. The genetic samples are taken with the help of buccal swabs or blood samples to avoid discomfort and reluctant participants. Statistical techniques of data analysis are highly valid and complex in nature. The regression analysis is employed to discover the connection of certain VDR polymorphisms and bone density with interactions from the age, gender, ethnic background, and other lifestyle factors. Mean bone density is compared by using Analysis of Variance (ANOVA) while other factors that may affect bone density are tested using multivariate analysis, in which more than one variable is tested at the same time. The influence of other factors needs to be eliminated, and various methods like multivariable regression models analyse the data to check the impact of confounding factors and ensure that the results obtained are correct and the variations in the scores of bone densities are indeed due to the variations in VDR polymorphisms [8]. The study designs based on clear inclusion criterion with appropriate significant difference, the use of novel genetic analysis method, the precision of measurement of bone density, the rigorous definition of statistical analysis collectively offers a higher level of scientific understanding on how VDR gene influences the bone density. As such, this methodology seeks to identify genetic aspects that may cause or affect bone health, and therefore identify better ways in which such diseases like osteoporosis could be prevented or managed. With the current approach of incorporating both genetic information and environmental and lifestyle factors, [9] this line of study aims to comprehensively illustrate regulation of bone density while creating a foundation of doing further studies and developing new therapies to improve bone quality and human life of multiple populations [10].

Results

Consequently, the results defined in this study are concerned with the efficiency of polymorphisms in the VDR gene and how they affect bone density. Several works have focused on the frequency of unique polymorphisms, including FokI, BsmI, ApaI and TaqI, concerning the bone mineral density. These studies show that the frequency of these polymorphisms exhibited in different populations could be quite different. For example, the FokI polymorphism might be predominant with specific ethnic groups; the BsmI polymorphism in other ethnic group [11]s. These polymorphisms' impacts on bone density are described by statistical values such as odds ratios and confidence intervals which shows the magnitude of associations. The p-values of a study define the significance by comparing the results of a study with the results of a sample of identical studies with those values being less than 0. 05 are normally accepted as being significant of the connection between the polymorphism and bone density. Observing the direct how various polymorphisms influence bone density it is possible to identify that impacts are rather diverse. For instance, FokI polymorphism seems to reduce bone mineral density and is a possible risk factor in osteoporosis according to some researchers. On the other hand, there is the BsmI polymorphism that has been associated with increased bone density thereby providing a protective function. Some of these differences can be explained to the effect of these polymorphisms on the function of VDR gene and therefore vitamin D metabolism and bone health use [12]. The same applies to the ApaI and TaqI polymorphisms which also demonstrate different results when it comes to bone density, which can be either positive or not affected at all. Such inverse associations demonstrate ambivalent relationship between genetics and bone health and call for more research in this area [13].

Collecting bone density data from the subjects belonging to different groups with and without specific polymorphisms also offer functional significance of those genetic differences. For example, individuals having FokI polymorphism can have lower degree of bone density than that of people without this particular biomarker for this polymorphism may be an actual genetic risk factor for osteoporosis, a condition characterized by low bone mass that predisposes a person for bone fractures [14]. On the other hand, people with BsmI may have better score in bone density than those without this biomarker because the absence or presence of this biomarker These comparisons are usually done using test statistics like the t-tests or ANOVA that assist in determining differences in the bone density between

groups. Specific details concerning the effects that are associated with each polymorphism are important in determination of the roles of genetic factors concerning bone health especially in view of the great potential that has been indicated for the concept of personalized medicine [15]. Comparative efficacy of various VDR polymorphisms is determined by statistical analyses that have a significant task within the context of the guidelines. For instance, regression analysis can exclude other influential factors including age, gender, ethic group, and lifestyles; thus determining the impact of the polymorphisms on bone density. This analysis can inform if some polymorphisms are more potent than others in affecting bone density and consequently if the impact differences between populations are distinct. One of the major advantages of using multivariate analysis is that more than one variable can be considered at a time, thus presenting a culmination of such factors while explaining genetic and environmental factors that affect bone health [16].

Additional studies of subgroup data continue the above findings; the effectiveness of various VDR polymorphisms is studied depending on the population. For example, while the direct effect of the FokI polymorphism on bone density exists, the reported difference in this factor might be significant in postmenopausal women as compared to younger women and men. Likewise, the BsmI genotype's protective effect could be masked in some ethnic groups with greater inherent bone density risk. Subgroup analyses are required in order to discover the genetic susceptibility of populations and help design intervention programmes to enhance bone quality. Bone density outcomes are perhaps the most important variables that are under consideration in relation to the particular polymorphisms of interest in this study. Coefficients of relationship like Pearson's r are used to measure the intensity and direction of polymorphisms to bone density. A positive sign also points to the evidence in the context of the given polymorphism which means as the level of a particular polymorphism rises so does the bone density and on the other hand, a negative correlation holds the opposite view. These correlations offer helpful information about the functions of VDR genetics and the mechanisms that polymorphisms of VDR entail for bone density [17].

Therefore, the findings in this study have demonstrated that genetic polymorphisms play an important role in the regulation of skeletal mass through the VDR gene. The distribution and effect of these polymorphisms represented significantly between populations, so it reinforces that the genetic differences be taken into consideration in the investigation of bone health. To a certain extend, it is now believed that certain polymorphisms like FokI increase the risk of presentation of low bone density and development of osteoporosis while polymorphisms like BsmI may present an adaptive effect. These findings have significant application to the emerging concept of a tailor-made medicine, which hints at the fact that screening VDR polymorphisms could be of help to pinpoint individuals at high risk of bone density loss to enable the provision of custom-made prevention/supervision profiles. Future work is required to specify the impact of these polymorphisms on bone health and to identify the best way to apply genetic, lifestyle, and pharmacological approaches to achieve the maximum clinical benefits in bone density for people of various backgrounds [18].

Aspect of Comparison	**FokI Polymorphism**	**BsmI Polymorphism**
Effect on Bone Density	Reduces bone mineral density	Increases bone mineral density
Risk Association	Risk factor for osteoporosis	Protective function
Population Frequency	Varies among ethnic groups	

		Varies among ethnic groups
Significance (p-values)	Significant if $p < 0.05$	Significant if $p < 0.05$
Statistical Values	Odds ratios, confidence intervals	Odds ratios, confidence intervals

Discussion

The discussion section of this study provides an analysis of the findings related to the analysis of genetic polymorphisms that affect the VDR gene and bone density in line with prior studies and provides a discussion on the clinical relevance of these findings, strength and limitations of the relative and possible directions of future research. The rationale for emphasis on these findings as that their particular relation to the identified VDR polymorphisms and changes in bone density corresponds with previous research. For instance, the FokI polymorphism has often been associated with decreased bone density, this explains the genetic susceptibility to osteoporosis. On the other hand, these polymorphisms particularly the BsmI polymorphism are associated with improved bone density implying a protective influence. These affiliations establish the importance of heredity in the determination of bone density and provide further evidence for the assumption that genetic makeup of VDR gene may have variable impact on a person's odds of developing bone density-related disorders.

Based on the observations discussed earlier, the relationships between VDR gene polymorphisms and bone density could be linked to several possible mechanisms. The VDR gene possesses the vital activity of influencing the bone metabolism such as calcium absorption and bone mineralization regulated by vitamin D. Variability of this gene can cause changes in the structure and function of the vitamin D receptor protein and its ability to bind vitamin d and in turn, influence gene expression . For example, the FokI polymorphism leads to production of shorter and presumably less efficient receptor, which may decrease calcium intake and bone production. On the other hand, the BsmI polymorphism might in some way improve receptor function or number leading to improved calcium balance and consequently improved bone density. Such mechanisms draw attention to the interaction between genetic differences and bone status, stressing the requirement for additional investigation on those processes. Consequently, the practical implications of these discoveries are mainly within clinical practices and consist of the proposition that VDR gene polymorphism screening can be incorporated in the evaluation of a person's susceptibility to osteoporosis and similar conditions. The knowledge of subjects with FokI and other high-risk polymorphisms would allow their application of preventive/asymptomatic measures; diet, vitamins, and drugs for bone density decline prevention. Fitness programs, therapies and medications that are keyed on one's genotype could help to enhance a patient's therapeutic experience, since such a treatment plan would be founded on an understanding of their unique genetic profile and would therefore enhance bone health results. Moreover, there could be interventions that will be designed to fit the gaps … linked to polymorphism to increase the effectiveness of preventive and therapeutic measures related to a decrease in bone density.

However, the current study possesses the following drawbacks: The study's sample might be small to adequately estimate the gene variation and its effects on bone density, which is a limitation to the study's conclusion. However, the choice of participants and the methods of data collection may introduce certain bias into the results and thus, the findings should be viewed with a specific caution. The study also does not take into consideration the confounding factors which include the type of diet one takes, level of physical activity, and the amount of time one spends under the sun about factors that have been proved to affect bone density. These factors may in some way obscure the relationship between VDR polymorphisms and bone density and thus point to the fact that more extensive studies have to be done regarding the variables. As a result, the future research should aim to resolve these limitations and try

to perform the research involving the participants of different ethnicities and ages. Therefore, the longitudinal investigations are found to be crucial in evaluating the consequences of VDR polymorphisms as well as, in the dynamics of BMD and the progression of disorders associated with bone density. It seems such investigations could offer promising ideas on how genetic components, epigenetic effects, and bone tissue quality interact and alter, which should help to produce better preventive and curative approaches. Further, the study should establish whether it is possible to use both genetic and other intercessions that extend from lifestyle alterations to pharmacological intercessions with the intent of getting the best results concerning bone health in different populations.

Conclusion

Thus, the present research proves the role of VDR gene polymorphisms as a strong mediator in determining the density of bones while emphasising on the advantages and disadvantages of certain genotypes. One can note that the variations in certain genes, which include FokI and BsmI, have a sufficient impact on the rate of bone health and reflect the priori perspective on the possibilities of the development of a personalized medicine. The incorporation of genetic screening for VDR polymorphisms should be made part of routine clinical treatment to ensure that people with potential tendencies toward osteoporosis and similar diseases that relate to bone density should be efficiently detected and managed properly. Further prospective studies are required to elucidate the molecular foundations linked to bone quality and to enhance the modality of the treatment to enhance the outlook of the patient. Thus, there is deserved emphasis on the ongoing research and discovery in this area for the improved and personalized approach to the specific population groups' bone health.

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