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Review Article

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VDR Gene and Bone Mass

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Abstract

Background: In recent years, the relevance of vitamin D receptor (*VDR*) gene restriction fragment length polymorphisms and BMI has been investigated by a great number of studies. It has been hypothesized that *VDR* polymorphisms may influence the bone mass. However, studies investigating the associations between specific *VDR* polymorphisms and bone mass often show controversial results. We have now performed a systematic review of the literature to analyse the relevance of *VDR* polymorphisms for bone mass.

Materials and methods: An analysis of studies evaluating the association between vitamin D receptor gene polymorphisms Fok1, Bsm1, Taq1, Apa1, and Cdx2, poly (A) and Bgl1 as well as some haplotype combination has been performed. Data were extracted from PubMed using the key words *VDR* polymorphism in combination with bone mass.

Results: This analysis was performed with the intent of giving an up-to-date overview of all data concerning the relevance of *VDR* polymorphisms for bone mass. Obviously, at present it is still not possible to make any definitive statements about the importance of the *VDR* genotype for bone mass. It seems probable that interactions with other factors such as calcium and vitamin D intake, 25(OH)D plasma levels and others gene play a decisive role in BMI occurrence and should not be underestimated. Other risk factors such as obesity, smoking status, alcohol and others are also frequently mentioned as being more or less important for BMI depending on the *VDR* genotype.

Conclusion: The determination of the *VDR* is hardly usable test from the point of view of clinical practice. The association between *VDR* and bone mass is relatively small overall. To date, however, the role played by the *VDR* gene polymorphisms on bone mass has not been defined with precision and requires a further confirmation in larger population groups, better characterized and different from ethnic point of view. Probably other and environmental factors involved in determining bone mass have yet to be identified.

Keywords: Osteoporosis gene; Skeleton and bone loss; Osteoporotic fractures; Skeletal metabolism

Introduction

The pertinence of nutrient D receptor (*VDR*) quality limitation section length polymorphisms and BMI has been explored by an incredible number of studies. It has been conjectured that *VDR* polymorphisms may impact the bone mass. We have now played out a precise survey of the writing to examine the significance of *VDR* polymorphisms for bone mass. An examination of studies assessing the relationship between nutrient D receptor quality polymorphisms Fok1, Bsm1, Taq1, Apa1, and Cdx2, poly (A) and Bgl1 just as some haplotype mix has been performed. Information was collected from PubMed utilizing the catchphrases *VDR* polymorphism in blend with bone mass. This examination was performed with the aim of surrendering a to-date outline of all information concerning the pertinence of *VDR* polymorphisms for bone mass. Clearly, at present it is as yet unrealistic to offer any complete expressions about the significance of the *VDR* genotype for bone mass. It appears to be likely that communications with different factors, for example, calcium and nutrient D admission, 25(OH) D plasma levels and others quality assume an unequivocal part in BMI event and ought not be thought little of. Other danger factors like weight, smoking status, liquor and others are likewise much of the time referenced as being pretty much significant for BMI relying upon the *VDR* genotype. The assurance of the *VDR* is not really usable test according to the perspective of clinical practice. The relationship among *VDR* and bone mass is generally little by and large. Until now, in any case, the pretended by the *VDR* quality polymorphisms on bone mass has not been characterized with exactness and requires a further affirmation in bigger populace gatherings, better described and unique in relation to ethnic perspective. Presumably other and ecological variables engaged with deciding bone mass still can't seem to be distinguished.

Research Osteoporosis Gene

Genetic factors play an important role in the pathogenesis of osteoporosis. Studies on twins and on entire families have shown that between 75% and 85% of the variance of bone density (BMD) is under genetic control Arden et al. In recent years considerable efforts have been made to discover the gene or genes of osteoporosis [1]. This research due to the multifactorial pathogenesis of osteoporosis led to many confusing and conflicting results between them.The pioneering work of Morrison et al. with the vitamin D receptor (*VDR*) represented a reasonable approach to find the candidate gene for osteoporosis for the relationship between vitamin D and skeletal metabolism [2]. After several other studies have confirmed the association between

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VDR and bone mass. However, the complex biology of the skeleton and bone loss tied to age makes it very unlikely that only one gene involved in the disease. Another gene widely studied is that of type I collagen (COLIA1) for the fundamental role in the regulation of protein synthesis of demineralized bone matrix Grant et al. Later were investigated polymorphisms of candidate genes as the gene for calcitonin receptor (CTR) [3,4] and for estrogen receptor alpha (ERa) [5] Interleukin 6 (IL-6) the transforming factor-beta 1 (TGF-b1) the gene for Apo Lipoprotein E (APOE) and the gene Osteo Calcin (OC) [6]. All these genes have been associated with bone mass and/or the osteoporotic fractures in some populations, but not in others: at the moment there is still an almost incomplete knowledge of the meaning and the mechanism of action of these polymorphisms. According to studies analyzed the genetic markers explain only in small part the variance of BMD, and data on individual genes appear to be controversial. Are at least two reasons for the apparent discrepancy in the results of genetic studies on bone mass. The first reason is that many factors influence the peak bone mass achieved in adulthood. In fact, in addition to a genetic component is extremely variable, there is an equally variable component that derives from the events of life and that includes diseases, taking drugs, preset State and osteoporosis, diet, exercise, alcohol and smoking. It should be noted that even the loss of age-related bone mass and the speed of loss that varies individually (Garn) are other factors that can affect BMD values. The second reason that can clarify the controversy of genetic data is linked to nature and to the frequencies of genetic polymorphisms among various populations. One or more allelic variants show a relatively high prevalence in some ethnic groups, while they are less frequent in others. It is not surprising, therefore, that the different polymorphisms have different allele frequencies when analyzed in different populations. However, it is possible that associations between the allelic variants of these genes are sometimes observed and sometimes not, and sometimes in opposite directions are observed. It is not to be excluded that environmental factors have a strong impact on the genetic potential peak bone mass. In light of all these observations is necessary that studies be conducted on samples polymorphisms sufficiently adequate as a number, so they can be checked for multiple confounding factors.

Receptor (*VDR*) gene

The *VDR* gene is located on the long (q) arm of chromosome 12 at position 13.11. More precisely, the *VDR* gene is located from base pair 48, 235,319 to base pair 48, 298,813 on chromosome 12. The effects of vitamin D are mediated by nuclear receptor (*VDR*), which forms an eterodimerico complex with the Retinoic acid receptor and interacts with transcription factors. *VDR* (12q12-14) encodes a protein of 427 amino acids (aa), which regulates the transportation and homeostasis of calcium and has been proposed as the locus to greater genetic effect on BMD in association studies. There are several polymorphic sites in the region 3 ' of human *VDR* gene identified by restriction endonuclease TaqI and BsmI, and another polymorphic variant, recognized by FokI, presumed level of transcription initiation codon in Exon 2. Alleles are respectively called T-t, B-b and F-f: lowercase letters identify the presence of restriction site and letters indicate the absence of any such site. These polymorphisms can affect the response to various dietary components with potential risks of developing the disease, now amply demonstrated functional involvement of alleles of *VDR* in calcium homeostasis and bone mineralization. Initial studies have made it possible to see the interaction between the *VDR* gene, the calcium absorption and calcium levels in the diet. Allelic variations of *VDR* gene account for 70% genetic effects on bone density. Most of the effects of 1. $25(OH)_2$ D on target tissues is due to the binding of vitamin with a high affinity intracellular receptor that acts as a transcription factor activated by ligand. Studies on gene cloned from animals (mouse, chicken) and man made it possible to define the structure and functions of *VDR* which is constituted by: a) a portion located at the level of the end carbossiterminale that specifically recognizes Calcitriol, molecule b) from sites located in two regions zinc finger at aminoterminale, responsible for the formation of a heterodimer with the Retinoic acid receptor (RXR), c) a sequence repeated in connection with vitamin D, and finally, d) a reason, very similar in all the receptors of thyroid and steroid hormones, represented by the same zinc fingers that interact with specific DNA sequences in the promoters of genes regulated by transcript 1. $25(OH)_2$ D3. The *VDR*, 125 cc to vitamin D, you bind to RXR and undergoes allosteric modification that allows him to interact with nuclear proteins of the complex transcription start and in this way the RNA polymerase II which is an integral part [7]. The role of *VDR* as a mediator of 1. $25(OH)_2$ D can be influenced by many factors including: the availability of vitamin D, which depends on the balance between diet, Sintesi and catabolic processes; the contents of receptors in cells, which is governed by the *VDR* ligands and other hormones and growth factors; post-trascrizionali changes of *VDR* ligand-induced, such as serine residues devices that reduce the activity of the receptor itself. The level of the components of the complex of transcription in the nucleus (Figure 1)[8].

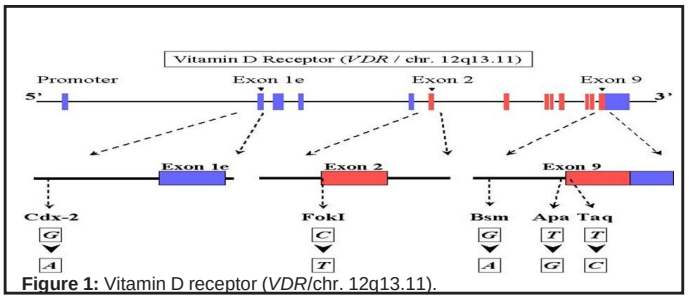

Figure 1: Vitamin D receptor (*VDR*/chr. 12q13.11).

Polymorphism and Osteoporosis

The *VDR* gene has been widely the subject of study in an attempt to explain the mechanisms involved in bone and inheritance to identify those predisposed to greater tissue loss. This knowledge, in fact, may have useful implications in terms of osteoporosis prophylaxis and treatment of patients who have an increased bone turnover and the risk of fracture (immobilization, chronic diseases, menopause, and transplantation). The main identifiable in *VDR* polymorphisms are four: most of them are located in non-coding gene regions (introns) and in itself does not alter the amino acidic structure of the receptor, but can interfere with the transcription of coding regions (exons) or mRNA stability. Restriction enzymes used were: BSM I, APO, Taq I and FOK; the first polymorphic site described was recognized by BSM I, located between Exon VIII and the 3' non-coding: the enzyme cuts the b allele but not the allele b. in 1992 Morrison et al. Observed a correlation between the genotype BB for the *VDR* gene and Osteocalcin levels in a group of healthy subjects, male and female not bound by ties of kinship, made more significant in post-menopausal women [2]. Morrison et al, the same Morrison and his colleagues investigated the distribution of two alleles of *VDR* gene in identical twins (MZ) and dizigoti (DZ): MZ were having a greater concordance for bone mineral mass compared to subjects with different (alleles is useful to remember that the MZ share all genes while the DZ only 50%) [2]. This study showed that the *VDR* could account for up to 75% of the total genetic effect on bone mass in healthy individuals, that the genotype was significantly correlated to BMD and, in particular, that the B allele was associated with lower BMD and b to higher values of BMD among both the twins both in the general population. The BB, so were disadvantaged in terms of BMD

and that genotype could be a negative prognostic factor for individual changes of BMD in learning. These results were confirmed by studies conducted in Japan on a sample of healthy women and in England [9,2]. A number of later works based on linkage studies in twins (linkage is the presence of associated inheritance between polymorphisms and bone mass phenotype) and freedom of Association in more or less large populations, in which it assessed the prevalence of alleles of the gene in question between unfamiliar subjects and correlation between phenotypic frequencies and bone mass phenotype have come to opposite conclusions on the relationship between *VDR* polymorphisms and BMD [10]. The causes must be sought in non-uniform selection criteria, in the low number of cases, in different phenotypic frequency distribution in the Caucasian and Asian, methodological factors and the possible influence of endogenous and exogenous factors, such as age, physical exertion, menopause, calcium intake and bone diseases degenerative type. In particular, as regards age, Riggs et al. Observed a closer association between genetic effect and BMD in girls than older ones [11]. This was confirmed by a meta-analysis conducted by Cooper et al. the result that the *VDR*-3 polymorphism ‘ presents a modest effect on the bone mass that tends to decline with advancing age [12]. The fact that the bone mineral mass is conditioned by the relationship between genetic and environmental factors seems increasingly clear by Krall et al. Examined the influence of introduction of calcium and the years that have passed since the beginning of menopause on the relationship between *VDR* alleles and bone loss [13]; the data showed a higher rate of loss in menopausal women BB than bb when the calcium dose taken was low. Even Ferrari et al. showed that the introduction of football and the genotype Bb was significantly related to the reduction of bone mass in lumbar spine in the elderly [14]. In addition, as Polygenic disease, osteoporosis recognizes the contribution of many genes, including the *VDR*, each of which has a modest effect individually or interacting with others. Among others the *VDR* polymorphisms have been described T/T recognized by the enzyme Taq I in Exon 9 which is closely associated with BSM I with respect to t and B alleles; another restriction is the site for the enzyme Apa in intron 7 between BSM I and Taq I, its alleles are YOY; Finally, a mutation There is the enzyme does not cut and is the longest protein synthesized starting from the first codon. Polymorphism is characterized by alleles F/f, f is the largest receptor, whereas F is the smallest. F genotype was associated with a lumbar spine BMD lower than FF in a population of Mexican-American women-menopausal Caucasian (Figure 2) [15].

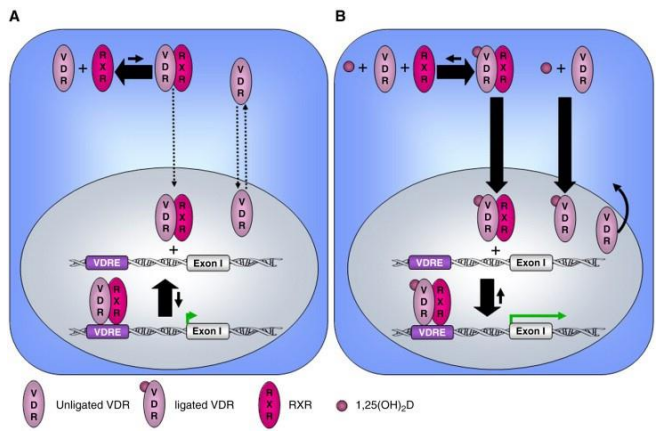

Figure 2: *VDR* and BMI.

Relation between *VDR* and BMI

Three have been *VDR* gene polymorphisms associated with bone density in some populations but not in others Cooper et al. Morrison Morrison et al. reported that the allelic variations of *VDR* gene account for 70% genetic effects on bone density in twins and showed a similar association in a group of 311 Australian women [12,2]. The higher density values were borne by the b allele, while the less frequent allele B is associated with lower BMD values.

The magnitude of the difference between group’s bb and BB at the level of column is approximately 10% (Figure 3).

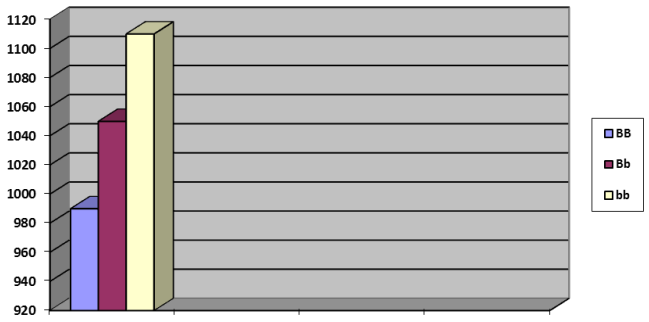

Figure 3: Difference between group’s bb and BB.

These figures have not been confirmed either by another American study on twins and even from further study of Morrison [2]. Only half of the studies published so far (50 between abstract and work “in extenso”) showed a significant association between *VDR* and bone mass, although differences in bone density for allelic variants of *VDR* appear modest. A meta-analysis on data from 16 of these studies revealed a weak association between alleles of the *VDR* and bone density values at the level of various skeletal sites, but the amount of the percentage difference between extreme genotypes are on average in the order of 2% (Table 1) (Figure 4) [12].

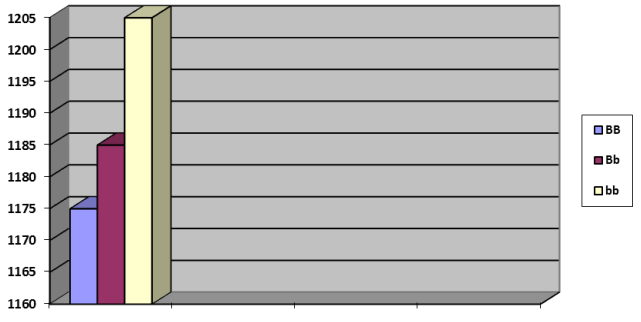

Figure 4: Lower bone mass in patients with genotype bb and modestly high in BB.

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Campinone studied	Skeletal sites	BB	bb	Δ%
Australian population	Column	0,99	1,11	10,8
Morrison et al. [4]				
N° 311 pre-postm	Femore	0,82	0,88	6,8
US population				
Studio Framingham	Colonna	1,14	1,20	5,0
Yanagi [5]				
N° 328 age> 68 years	Femore	0,76	0,79	3,7
Dutch population				
Studio Rotterdam	Colonna	1,03	0,97	5,8
Uitterlinden et al.[16]				
N° 1778 age> 65 years	Femore	0,82	0,79	3,6
French population				
Studio	Colonna	1,00	1,00	0,0
Grant et al. [3]				
N° 220 prem age 31-57 years	Femore	0,92	0,83	1,2
US population				
Studio SOF	Colonna	0,88	0,86	2,3
Riggs et al. [11]				
N° 531 age> 65 years	Femore	0,66	0,65	1,5
Grant et al. [3]				
Studio GIBIS 1999	Colonna	0,82	0,82	0,0
N° 295 pre-postm age 47-67 a	Femore	0,64	0,64	0,0

Table 1: Differences in bone density (%) between *VDR* genotypes.

In addition, some authors have found opposing associations: values of lower bone mass in patients with genotype bb and modestly high in BB [16]. It is reasonable to assume that these differences in the results of various studies depend from the differences concerning the size of the sample, age of subjects studied, ethnic origin and environmental factors. Has now acquired that take calcium and vitamin D may modify the effects of alleles of the *VDR* on calcium metabolism (Figure 5) [13,14].

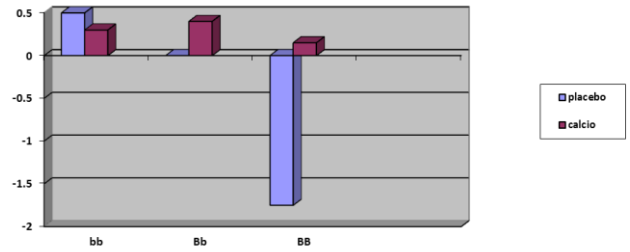

Figure 5: Relationship between the *VDR* and genotype bone mass is cloaked in populations with a high amount of calcium.

There are also indications to suggest that the relationship between the *VDR* and genotype bone mass is cloaked in populations with a high amount of calcium. The major effect of phenotypic variants of *VDR* seems to concern mainly the acquisition of bone mass at the end of development [9,2]. This means that an effect of the *VDR* could reverse with advancing age, however by some observations on elderly population and in particular from studies of twins, comes a claim an influence on bone loss in old age and to the persistence of genetic effects [13,14]. The risk of fracture after the age of 65 years may reflect the interaction between genetic and environmental heritage.

Conclusion

The determination of the *VDR* is hardly usable test from the point of view of clinical practice. The association between *VDR* and bone mass is relatively small overall. To date, however, the role played by the *VDR* gene polymorphisms on bone mass has not been defined with precision and requires a further confirmation in larger population groups, better Characterized and different from ethnic point of view. Probably other genes involved in determining bone mass have yet to be identified.

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