Relationship between vitamin D receptor gene (VDR) polymorphisms, vitamin D status, osteoarthritis and intervertebral disc degeneration.

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Review

Relationship between vitamin D receptor gene (VDR) polymorphisms, vitamin D status, osteoarthritis and intervertebral disc degeneration

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Cartilage
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A B S T R A C T

The vitamin D endocrine system is involved in bony and cartilaginous metabolisms and alterations in the homeostasis of this system could be associated to pathological conditions of cartilaginous tissue. In this context, the presence of polymorphisms in the vitamin D receptor gene (VDR), in association with the susceptibility to common osteochondral diseases, was largely investigated.

The aim of this review was to summarize data present in literature, analyzing the association of the VDR polymorphisms, vitamin D status and knee cartilage and intervertebral disc pathologies, trying to suggest links between the different specific pathologies analyzed.

Concerning the association between VDR polymorphisms and cartilaginous tissue diseases, we found controversial reports. However, the great majority of papers reported an association with lumbar disc degeneration, whereas about half of the studies found an association with osteoarthritis. A further association between VDR polymorphisms (in linkage disequilibrium) and the presence of specific characteristics of these diseases, in particular the formation of osteophytes, was evidenced.

Finally, the influence of vitamin D status on these pathologies was evaluated, trying to evidence the relation between the presence of particular genetic variants in the VDR and vitamin D levels or to show whether a particular vitamin D status could predispose to the development or progression of such diseases, however, no significant associations were found.

In the future, given the role of vitamin D system in the cartilaginous tissue metabolism, it could be interesting to perform functional and tissue specific studies to analyze the interplay between the different VDR variants and its ligand.

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1. Introduction

The vitamin D endocrine system and its major actors, the active vitamin D hormone, the vitamin D receptor (VDR), and the enzymes involved in the generation of the biologically active forms of the hormone, are involved in the modulation of different biological processes, including skeletal metabolism, immunological response, cancer-related metabolic pathways, proliferation and differentiation of a wide variety of cell types [1,2]. The known pleiotropic effects of vitamin D and its involvement in bony and cartilaginous metabolism could explain why alterations in vitamin D homeostasis are associated to several pathological conditions of knee cartilage and intervertebral disc tissue, in particular osteoarthritis (OA) and disc degeneration-linked pathologies, including lumbar disc degeneration (LDD), conditions on which we will focus our attention in the present review.

The influence of the variations in the DNA sequence of important proteins involved in the vitamin D system on specific pathophysiological processes can be analyzed by means of genetic studies. In this context, the VDR gene (VDR) is likely to be a candidate, since many polymorphisms (genetic variants with frequencies >1% in the human population) in this gene were identified. Several studies investigated the role of VDR polymorphisms in the susceptibility to common diseases (such as osteoporosis, OA and LDD), even if the real influence on VDR protein function and signaling in those pathologies is largely unknown.

Human VDR covers at least 105 kb, with an extensive promoter region capable of generating multiple tissue-specific transcripts [3,4]. Several biallelic polymorphic sites have been identified in the VDR sequence, both in the coding and noncoding region, the most known and studied are: BsmI, TaqI, Apal and FokI.

In Fig. S1 (supplementary data) are reported the structure of the genomic region, the location of the discussed SNPs and the haplotype blocks of the VDR. Table 1 shows formal and RFLP nomenclature for known SNPs in VDR considered in the review.

Supplementary material related to this article, found in the online version, at http://dx.doi.org/10.1016/j.jsbmb.2013.03.001.

Some of the cited sites, such as BsmI, Apal and TaqI, are located near the 3’ terminus of the gene and are in linkage disequilibrium (LD). BsmI and Apal apparently are not affecting any splicing site and/or transcription factor binding site.

TaqI represents a “synonymous” polymorphism in the coding sequence and, as the two polymorphisms mentioned above, it does not determine any change in the amino acid sequence of the encoded protein [5].

On the contrary, FokI is a C/T transition polymorphic site present in the VDR start codon [6]; the allelic variants of this polymorphism code for structural different receptor proteins (from a 424 aa wild type to a 427 aa long protein forms). This polymorphism can be considered independent and directly associated with pathological conditions, since there is no LD with any of the other cited polymorphisms and the LD area surrounding this polymorphism seems to be very small [3]. Consequentially, most functional studies have been performed exclusively on FokI.

The FokI polymorphism contribution to disease may be explained by the structural modification of the VDR protein following to the change on the transcription start site. However, no differences were observed between the two receptor forms for what concern ligand affinity and DNA binding [7]. Other studies suggested that this polymorphism could be associated to a different efficiency of VDR binding with the transcription factor II B (TFII B) and, thus, to a different ability to induce transcription of vitamin D dependent genes [8,9], with the shorter wild protein interacting more efficiently with TFII B [3,10,11] and showing a higher transcriptional rate. Thus, FokI polymorphism seems to affect in some ways the function of the encoded protein and it could be interesting to study the consequent effect of this on specific vitamin D target genes and/or whether these effects are peculiar for specific cell types or tissues.

Apart from FokI polymorphism, many association studies have been focused on the 3’ regulatory region of the VDR which contains polymorphisms probably not affecting the VDR protein, but likely in LD with other nearby functional ones, which, at turn, could be responsible for the observed associations of such VDR polymorphisms with several pathological phenotypes [3]. In particular, the VDR lies downstream from the collagen type II alpha 1 (COL2A1) gene, with a close LD between VDR and a COL2A1 haplotypes [12]. Since the COL2A1 product is abundantly present in cartilage, the main target tissue in OA, it was proposed as a candidate gene to explain the associations between this pathology and DNA sequence variations. However, although the gene has been implicated in OA [13-15], controversy remains [16,17].

In recent years, some authors suggested to analyze the polymorphisms in the relevant areas of the VDR and to determine how they are interacting with each other in both genetic and functional terms, particularly using different cell types, which could help in clarifying the molecular mechanisms underlying the associations observed between them and different diseases. In this context, although subjects might have identical genotypes for a number of Single Nucleotide Polymorphisms (SNPs) across a gene, the different bio-responses could be related to different haplotypes spanning in the same gene or in different genes [3].

1.1. VDR polymorphisms and osteoarthritis

Osteoarthritis is a disease, affecting primarily knees, hips, hands and spine, characterized by degeneration of articular cartilage and causing chronic pain and disability [18], with a largely unknown pathogenesis. Different environmental factors, including obesity [19,20], previous injury [21], mechanical stress [22,23] and other metabolic factors [24], have been associated with this condition, but a genetic contribution to OA has been suggested in several epidemiologic studies [25].

In this context, one of the candidate genes analyzed was the VDR but, since there are inter-racial differences in the distribution frequency of VDR polymorphisms [5,26,27], SNPs association with the development of OA, in different population, is controversial [28-32].

Apart from the influences of the ethnic origin, absence of consistent findings may be partly due to the different anatomical joints studied, to variations in environmental factors related to vitamin D metabolism, and/or to the presence of other (still unknown) genetic factors that potentially influence VDR function.

Table 1 summarizes all the studies from 1997 to 2011, reporting or not a significant association between knee, hip, hand or spine OA with known VDR polymorphisms or haplotypes.

In particular, Apal, TaqI, BsmI, FokI, Cdx2 polymorphic restriction sites, with special interest in BsmI, Apal, and TaqI polymorphisms, were studied, with focus on the mutated BsmI and Apal alleles combined with the wild TaqI allele, the baT haplotype.

Table 1 Nomenclature for known SNPs in VDR considered in the review. Formal nomenclature for SNPs was obtained from NCBI database of SNPs (http://www.ncbi.nlm.nih.gov/snp?term=vdr%20home).

<table>
<thead>
<tr>
<th>RFLP Nomenclature</th>
<th>Reference SNPs</th>
<th>RFLP alleles</th>
<th>Location on VDR</th>
</tr>
</thead>
<tbody>
<tr>
<td>BsmI</td>
<td>rs1544410</td>
<td>B/b</td>
<td>Intron 8</td>
</tr>
<tr>
<td>TaqI</td>
<td>rs731236</td>
<td>T/t</td>
<td>Exon 9</td>
</tr>
<tr>
<td>Apal</td>
<td>rs7975232</td>
<td>A/a</td>
<td>Intron 8</td>
</tr>
<tr>
<td>FokI</td>
<td>rs10735810</td>
<td>F/f</td>
<td>Exon 2</td>
</tr>
</tbody>
</table>
Table 2
Characteristics of studies (case/control and population-based) analyzing VDR polymorphisms and OA.

<table>
<thead>
<tr>
<th>Study design</th>
<th>Affected sites</th>
<th>Country (ethnicity)</th>
<th>Population</th>
<th>Males/females</th>
<th>Age (males/females)</th>
<th>Type(s) of VDR polymorphism(s)/haplotypes</th>
<th>Association</th>
<th>Study (Ref.)</th>
<th>OR; 95%CI; p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case/control study</td>
<td>Knee</td>
<td>UK</td>
<td>82 cases, 269 controls</td>
<td>Postmenopausal females</td>
<td>58.3 ± 4.7 cases, 54.4 ± 4.8 controls</td>
<td>TaqI polymorphism</td>
<td>Yes</td>
<td>[28]</td>
<td>Allele T associated with an increased risk of OA (OR = 2.82, 95%CI = 1.16–6.85, p = 0.02)</td>
</tr>
<tr>
<td>Case/control study</td>
<td>Hip</td>
<td>Belgium</td>
<td>75 patients who underwent total hip replacement, 239 controls</td>
<td>Postmenopausal females</td>
<td>75 ± 5 cases, 70 ± 6 controls</td>
<td>BsmI polymorphism</td>
<td>No</td>
<td>[33]</td>
<td>–</td>
</tr>
<tr>
<td>Case/control study</td>
<td>Hand, hip, knee</td>
<td>Japan</td>
<td>134 cases and 136 controls</td>
<td>All females</td>
<td>63.8 (29–87) cases, 72.2 (60–90) controls</td>
<td>BsmI, Apal and TaqI polymorphisms/haplotypes</td>
<td>No</td>
<td>[31]</td>
<td>–</td>
</tr>
<tr>
<td>Case/control study</td>
<td>Total hip or knee replacement</td>
<td>UK</td>
<td>371 cases, 369 controls</td>
<td>155/216 cases, 221/148 controls</td>
<td>74 (56–80)/72 (56–90) cases, 74 (61–89)/71 (59–88) controls</td>
<td>TaqI polymorphism</td>
<td>No</td>
<td>[36]</td>
<td>–</td>
</tr>
<tr>
<td>Case/control study</td>
<td>Hip</td>
<td>Italy</td>
<td>143 cases/50 controls</td>
<td>40/103 cases, 15/35 controls</td>
<td>64 (22–88) cases, 67 (50–70) controls</td>
<td>BsmI polymorphism</td>
<td>Yes</td>
<td>[34]</td>
<td>Higher frequency of bb genotype (45.2%) in patients with developmental hip dysplasia compared with controls (34%), p = 0.05</td>
</tr>
<tr>
<td>Case/control study</td>
<td>Knee</td>
<td>UK</td>
<td>603 knee OA, 596 controls</td>
<td>298/305 knee OA, 300/296 controls</td>
<td>72.1 ± 6.9/73.5 ± 7.16 cases, 71.0 ± 7.8/72.1 ± 8.5 controls</td>
<td>Fold and TaqI haplotype</td>
<td>Yes</td>
<td>[40]</td>
<td>Association of ftt haplotype with higher OA risk in men (OR = 1.99, 95%CI = 1.46–2.78)</td>
</tr>
<tr>
<td>Case/control study</td>
<td>Knee, hip</td>
<td>UK</td>
<td>1040 knee OA, 1004 hip OA, 1123 asymptomatic controls</td>
<td>535/505 knee OA, 497/507 hip OA, 601/522 asymptomatic controls</td>
<td>68.1 ± 7.4 knee OA, 67.7–7.1 hip OA, 64.3 ± 8.4 asymptomatic controls</td>
<td>Fold, Apal, TaqI polymorphisms</td>
<td>No</td>
<td>[42]</td>
<td>–</td>
</tr>
<tr>
<td>Prospective, population-based cohort study</td>
<td>Knee</td>
<td>The Netherlands</td>
<td>846 elderly</td>
<td>405/441</td>
<td>68.6 ± 6.9/68.5 ± 6.8</td>
<td>bAt, BaT, bAt haplotypes</td>
<td>Yes</td>
<td>[29]</td>
<td>Association of baT haplotype with OA (OR = 2.27, 95%CI = 1.46–3.52)</td>
</tr>
<tr>
<td>Prospective, population-based cohort study</td>
<td>Knee</td>
<td>The Netherlands</td>
<td>851 elderly</td>
<td>407/444</td>
<td>68.5 ± 6.9/68.6 ± 6.8</td>
<td>bAt haplotype, COL2A1 4B polymorphism</td>
<td>Yes</td>
<td>[30]</td>
<td>Increased risk to develop OA for baT haplotype carriers (OR = 1.78, 95%CI = 1.02–3.12); higher risk showed by carriers of both COL2A1 4B allele and VDR bAt haplotype (OR = 2.68, 95%CI = 1.41–5.10)</td>
</tr>
</tbody>
</table>
Concerning BsmI polymorphism (wild B to mutated b allele), controversial results were reported. No significant contribution of this SNP to hip [33] or to hand or knee OA, osteophytes and joint space narrowing (JSN) was observed [32]. However, a significant higher frequency of homozygous bb in patients affected by developmental hip dysplasia was found [34]. Whereas, another study highlighted an association of the B allele with the severity of osteophytes in lumbar spine OA patients [35].

Interestingly, the VDR wild allele T of the TaqI polymorphism was associated with an increased risk of knee OA compared with the mutated t allele, independently by age, BMI, BMD [28]. Nevertheless, in other two UK studies, no association was reported between knee OA, the presence of osteophytes, JSN and TaqI polymorphism [36,37].

In addition, no association between Apal and TaqI polymorphisms and the overall risk of hand OA was found by a Finnish women study, but symmetrical OA was associated with carriage of the AT haplotype and low calcium intake [38].

In two studies [29,30] performed on the same Dutch population of elderly males and females subjects selected from the Rotterdam Study, Uitterlinden and colleagues reported a significant overrepresentation of the baT haplotype in individuals with the OA disease. In the first of these two works they showed an association of baT haplotype with knee OA, independently from bone density, while baT haplotype was found to be associated with reduced prevalence of OA and modestly reduced bone density. In the second study, they confirmed the previously observed association, also analyzing the role of COL2A1 4B allele. They showed that VDR baT carriers had an increased risk to develop OA and that a higher risk was showed by carriers of both COL2A1 4B risk allele and VDR baT haplotype. The frequency distributions of BsmI, Apal and TaqI RFLPs were also examined in Japanese female patients affected by hand, hip, tibiofemoral, patellofemoral or polyarticular OA and compared with controls [31]. Neither significant differences in VDR genotype frequencies of each polymorphism nor in the distribution of the combined BsmI, Apal and TaqI genotypes were observed between controls and OA subjects.

A meta-analysis [39] studying the association between VDR TaqI, BsmI, Apal polymorphisms and OA including 10 relevant studies, 7 European and 3 Asian population studies, involving in total 1591 patients and 1781 controls was performed. Of these, 9 studies were conducted on VDR TaqI polymorphisms, 6 on BsmI polymorphisms, 5 on Apal polymorphisms [39]. The meta-analysis authors found no associations between VDR variation and OA. However, the study had some limitations, comprising the absence of subgroup analysis by OA site due to the different site of OA collectively examined, the heterogeneity in clinical features affecting the development of OA, the heterogeneous criteria for OA definitions and the non homogeneous, but rather restricted (European and Asian), ethnic groups tested.

FokI polymorphism was studied in association with other VDR SNPs. In a study, the haplotype formed by the 2 minor alleles of FokI and TaqI polymorphisms was associated with a significantly higher risk of knee OA in men [40].

Recently, another study [41] examined the association of the radiographic features of knee OA and knee pain with vitamin D level and VDR FokI, Cdx2 and Apal polymorphisms at the same time. There were no associations of these polymorphisms with the pathology, except for Aa compared with AA genotype of Apal, after adjustment for age, gender and BMI. Moreover, concerning the association of VDR polymorphisms and knee pain, the authors evidenced that the minor F homozygous genotype for FokI and AA homozygous genotype for Cdx2 polymorphism were significantly associated with higher prevalence of knee pain compared with FF for FokI and GG for Cdx2, while, rather surprising, Apal polymorphisms were not significantly associated with pain.
Finally, Limer and colleagues [42] attempted to the replication of the findings on genes reported to have significant genetic association with OA. In the “Genetics of OA and Lifestyle” (GOAL) study they compared allele or genotype frequencies of TaqI, FokI and Apal in controls and knee and hip OA subjects and did not confirm the previously reported associations with OA phenotypes for any of the studied polymorphisms.

1.2. VDR polymorphisms and lumbar disc degeneration

Low back disorders represent common musculoskeletal problems causing disability and 50–80% of adults experiencing at least one episode of low back pain (LBP) during the lifetime [43].

LDD is considered to be the primary cause of LBP [44,45] and it has a complex etiology. Many environmental and constitutional risk factors, including age, gender, weight, occupational load, smoking and exposure to vehicular vibration [46–51] probably contribute to the genesis or to the acceleration of spinal degeneration. Conversely, epidemiologic studies and reports among families and twins concluded that sciatica, disc herniation and disc degeneration may be largely explained by genetic factors, with a relatively minor effects of environmental and constitutional risk factors [52–55]. Other studies supported the idea that disc degeneration disorders may be genetically determined and there is a familiar predisposition for their development [53,56–61].

VDR is one of the most studied genetic factor supposed to be linked to intervertebral disc disease (IDD): the first association between polymorphisms in this gene and IDD, in humans, was reported in 1998. Low MRI signal intensity of thoracic and lumbar disc was associated with TaqI genotypes of VDR and a similar MRI pattern was observed for bulging and disc height in association with particular TaqI and FokI genotypes [62].

The interplay of occupational load exposure with a particular VDR genotype, in exaggerating the development of IDD, was also explored, but the results were controversial.

In train engineers, with an average of 21-years exposure to whole body vibration, and paper mill workers, with no exposure to vibration, no significant differences were found in the genotype frequencies of VDR TaqI and FokI between IDD phenotype and asymptomatic individuals, but whole-body vibration had significant interaction with SNPs in VDR, suggesting an additive effect of vibration and genetic risk factors for IDD phenotype [63].

In a cross-sectional genotype–phenotype evaluation of the same cohort no significant association between Modic changes and TaqI or FokI polymorphisms of VDR was observed [64].

A case-control study involving low back pain patients and controls revealed that family history of IDD, back injury history, whole body vibration, bending/twisting, heavy physical workload, age, mutation allele 5A of MMP-3 and A of VDR-Apal were significantly associated with LDD. Synergistic interactions existed between the mutation allele 5A of MMP-3 and whole-body vibration exposure or bending/twisting and the mutation allele A of VDR and bending/twisting, suggesting that subjects whom carry these mutation alleles are more vulnerable to IDD when exposed to whole-body vibration and/or bending/twisting [65].

The association of disc degenerative signs or pathologies and VDR genotypes was also analyzed in different populations. In young Japanese adults in their twenties, non-obese and no heavy manual labor, with or without low back problems, the Tt allele was found to be more frequently associated with an increased risk for disc disease at an early age, multilevel disc disease, severe disc degeneration and disc herniation than was the TT allele [66].

In contrast, the frequencies of T and t alleles did not correlate with disc degeneration and osteophyte formation in elderly Japanese females [67]. However, in a Japanese cohort of post-menopausal females affected by lumbar spondylosis, significant differences were reported in the severity of the pathology among Apal and BsmI haplotypes of VDR, especially in the upper levels of the lumbar spine. Of note, the association of the VDR haplotypes was more significant in the older (>63.6 years) than in the younger (≤63.6 years) group [68].

FokI polymorphism was analyzed in another cohort of elderly Japanese males and females with LBP, but no association between this polymorphism and osteophyte formation without disc degeneration was reported [69].

The same polymorphism was investigated in a case (patients with discopathies)/control study, showing that the f allele and the FF genotype frequencies were significantly higher in patients than in controls, while the FF genotype was higher in control subjects. Moreover, patients carrying the f allele showed a correlation with the increasing severity degree for disc degeneration and the age at the disease onset has shown to be early in individuals with –ff genotype [70].

FokI was studied also in combination with TaqI polymorphism in young Turkish patients with hernia or disc degeneration, but no significant differences between cases and controls for the alleles frequencies of VDR were observed [71]. However, the wild FF and TT homozygous genotypes were associated with mild forms, while tt, ff and FF alleles with the severe form of disc degeneration. An association was found in the patients having TT, Tt, FF and Ff genotypes with the protrusion type of disc herniation, whereas the patients having tt and ff genotypes were associated with extrusion/sequestration types of the disease [71]. The same polymorphisms were evaluated in a Norway case (LBP patients)/control study, but no associations with the pathology were reported [72].

Regarding the association of specific VDR SNPs and disc pathological features, a linear decrease in the risk of spinal osteophytosis, both presence and severity, and presence of disc space narrowing (DSN) from tt to TT genotypes was showed, independently by bone density [73].

In a Finnish population [74], it was evidenced that, in the L4–S1 discs, men with the tt TaqI genotype had more anular tears and the prevalence of osteophytes was lower in men with the tt and Tt genotypes, respectively, compared with those with the TT genotype. Conversely, in the L1–L4 discs, the prevalence of disc bulges was lowest in men with the tt genotype and subjects with this genotype also had a tendency toward fewer lumbar disc herniation compared with those with the TT genotype. Bone density, disc height and herniation did not differ significantly by genotype [74].

In another study it was observed that degenerative disc features and disc bulge developing, especially in individuals younger than 40 years, were significantly associated with the t TaqI allele of VDR, whereas anular tears and Schmorl’s nodes were not [75].

Finally, no association was found in a Finnish population between lumbar spinal stenosis (LSS) and TaqI or FokI polymorphisms in VDR [76], while association between the TaqI polymorphism and change in osteophyte grade was reported in LDD females from UK [77].

Table 3 summarizes all the studies from 1998 to 2012, reporting the association between LDD and VDR polymorphisms or haplotypes.

1.3. VDR polymorphisms and osteophytes in OA and LDD

The VDR is expressed in osteoblasts [78], chondrocytes [79], and intervertebral disc cells [80,81], cell types which can be found in the osteophytes [82], osseous and cartilaginous neoplastic protrusions displaying many of the stages of human bone turnover and remodeling [82,83]. In vitro experiments confirmed that loss of VDR in chondrocytes reduced osteoclastogenesis, by inducing receptor activator of NF-κB ligand (RANKL) expression [84], indicating that polymorphism of this gene may affect osteophyte formation.
<table>
<thead>
<tr>
<th>Study design</th>
<th>Disease/disease related characteristics</th>
<th>Country (ethnicity)</th>
<th>Population</th>
<th>Males/females</th>
<th>Age (males/females)</th>
<th>Type(s) of VDR polymorphism(s)/Haplotypes</th>
<th>Association</th>
<th>Study (Ref.)</th>
<th>OR; 95%CI; p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case-control study</td>
<td>Lumbar spinal stenosis</td>
<td>Finland</td>
<td>29 cases/56 controls</td>
<td>14/15 cases</td>
<td>59 (42–75) cases, 56 (22–72) controls</td>
<td>TaqI, FokI polymorphisms</td>
<td>No</td>
<td>[76]</td>
<td>–</td>
</tr>
<tr>
<td>Large scale, case/control study</td>
<td>Lumbar degenerative disc disease</td>
<td>China</td>
<td>388 cases/191 controls</td>
<td>Males and females</td>
<td>18–55</td>
<td>TaqI polymorphism</td>
<td>Yes</td>
<td>[75]</td>
<td>t allele associated with: degenerative disc disease (OR = 2.61, 95% CI = 1.15–5.90, p = 0.041), in individuals younger than 40 years (OR = 5.97, 95% CI = 1.69–21.15, p = 0.002); disc bulge (OR = 7.17, 95% CI = 1.43–36.01, p = 0.001)</td>
</tr>
<tr>
<td>Case/control study</td>
<td>LBP</td>
<td>Japan</td>
<td>387 elderly (Group A, 217 = osteophyte formation with disc height narrowing, Group B, 99 = osteophyte formation without disc height narrowing, Group C, 71 = cases without osteophyte formation)</td>
<td>153/234</td>
<td>Group A 68.9 ± 6.2, Group B 67.8 ± 6.2, Group C 65.5 ± 6.6</td>
<td>FokI polymorphism</td>
<td>No</td>
<td>[69]</td>
<td>–</td>
</tr>
<tr>
<td>Occupational cohort study</td>
<td>LBP</td>
<td>Finland</td>
<td>150 train engineers (cases), 61 paper mill workers (sedentary job)</td>
<td>All males</td>
<td>38–56 cases, age matched controls</td>
<td>TaqI, FokI polymorphisms</td>
<td>No</td>
<td>[63]</td>
<td>–</td>
</tr>
<tr>
<td>Case/control study</td>
<td>Discopathies associated or not with hernia</td>
<td>Brazil</td>
<td>66 cases/88 controls</td>
<td>–</td>
<td>38 (16–62) cases, 41 (16–57) controls</td>
<td>Fold polymorphisms</td>
<td>Yes</td>
<td>[70]</td>
<td>f allele frequency higher in patients (0.46) than in controls (0.15), p = 0.0001; FF genotype frequency higher in controls (69.3%) than in patients (13.6%), p = 0.0001; Ff genotype frequency higher in patients (81.8%) than in controls (30.7%), p = 0.0001; correlation of –/f and F/F genotypes with severity of disc degeneration (28.8%, 0.0%, respectively, p = 0.0012)</td>
</tr>
<tr>
<td>Occupational cohort study</td>
<td>Modic changes in endplates or lumbar vertebral bodies</td>
<td>Finland</td>
<td>159 train engineers (cases), 69 paper mill workers (sedentary job)</td>
<td>All males</td>
<td>46.0 ± 3.2 (38–53) cases, 47.8 ± 4.5 (36–56) controls</td>
<td>TaqI, FokI polymorphisms</td>
<td>No</td>
<td>[64]</td>
<td>–</td>
</tr>
<tr>
<td>Study design</td>
<td>Disease/disease-related characteristics</td>
<td>Country (ethnicity)</td>
<td>Population</td>
<td>Males/females</td>
<td>Age (males/females)</td>
<td>Type(s) of VDR polymorphisms/Haplotypes</td>
<td>Association</td>
<td>Study (Ref.)</td>
<td>OR; 95%CI; p value</td>
</tr>
<tr>
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<tr>
<td>Case-control study</td>
<td>LDD</td>
<td>China</td>
<td>178 cases/284 controls</td>
<td>64/94 cases, 96/188 controls</td>
<td>48.5 ± 13.1 cases, 40.6 ± 15.8 controls</td>
<td>TaqI, ApaI, MMP3 5A polymorphisms</td>
<td>Yes</td>
<td>[65]</td>
<td>AA/Aa genotypes in 54.93% controls and 67.42% cases; OR = 1.70, 95%CI = 1.15–2.51</td>
</tr>
<tr>
<td>Case/control study</td>
<td>LBP</td>
<td>Turkey</td>
<td>300 adults (150 cases and 150 controls)</td>
<td>–</td>
<td>20–30</td>
<td>TaqI, FokI polymorphisms</td>
<td>Yes</td>
<td>[71]</td>
<td>TT and FF genotypes associated with mild disc degeneration (p &lt; 0.001); tt, Ff, ff genotypes associated with severe degeneration (p = 0.048; p = 0.004; p = 0.041); TT, Ti, FF, Ff genotypes associated with protrusion (p &lt; 0.001); tt, ff genotypes associated with extrusion/sequestration (p = 0.023; p = 0.008)</td>
</tr>
<tr>
<td>Case/control study</td>
<td>LDD</td>
<td>Norway</td>
<td>146 cases/188 controls</td>
<td>66/80 cases, 50/50 controls</td>
<td>53.2 (30–76) cases, 39.3 (24–56) controls</td>
<td>TaqI, FokI polymorphisms</td>
<td>No</td>
<td>[72]</td>
<td>–</td>
</tr>
<tr>
<td>Random cross sectional population-based study</td>
<td>Spinal degenerative disease</td>
<td>Australia</td>
<td>282 subjects</td>
<td>110/172</td>
<td>69.3 ± 6.4/69.6 ± 6.4</td>
<td>TaqI polymorphism</td>
<td>Yes</td>
<td>[73]</td>
<td>Presence of osteophytosis: OR TT vs tt = 0.47, 95%CI = 0.19–1.16; severity of osteophytosis: OR TT vs tt = 0.41, 95%CI = 0.17–0.97; presence of DSN: OR TT vs tt = 0.45, 95%CI = 0.20–0.99</td>
</tr>
<tr>
<td>Population-based twin cohort study</td>
<td>Spinal degeneration</td>
<td>Finland</td>
<td>85 pairs (170 subjects)</td>
<td>All men</td>
<td>49.7 ± 8.2 (35–69)</td>
<td>TaqI, FokI polymorphisms</td>
<td>Yes</td>
<td>[62]</td>
<td>Signal intensity of thoracic and lumbar discs: 12.9% and 4.5% worse in men with tt and Tt compared with TT genotype (p = 0.003); 9.3% and 4.3% worse in men with ff and Ff compared with FF genotype (p = 0.006). Summary scores of signal intensity, bulging and disc height: 4.0% and 6.9% worse in men with FF and Ff compared with FF genotype (p = 0.029)</td>
</tr>
<tr>
<td>Study Type</td>
<td>Region/Location</td>
<td>Sample Size</td>
<td>Sex Distribution</td>
<td>Age</td>
<td>Genotype</td>
<td>Polymorphism</td>
<td>Results</td>
<td></td>
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<tr>
<td>Population-based twin cohort study</td>
<td>L4–S1 region: reduced signal intensity 14.3% lower in men with tt compared with TT genotype, ( p &lt; 0.001 ); annular tears 13.1% more in men with tt compared with TT genotype ( (p = 0.047) ); prevalence of osteophytes 7.5% and 3.3% lower in men with tt compared with TT genotype ( (p &lt; 0.001) ).</td>
<td>Finland</td>
<td>71 pairs (142 subjects)</td>
<td>All men</td>
<td>48.9 ± 8.1 (35–69)</td>
<td>TaqI polymorphism</td>
<td>Yes ([74])</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Population based study</td>
<td>LBP Japan</td>
<td>205 young adults</td>
<td>39/166</td>
<td>–</td>
<td>TaqI, Apal polymorphisms</td>
<td>No ([66])</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Population based study</td>
<td>Lumbar spondylosis Japan</td>
<td>318 post-menopausal women</td>
<td>All females</td>
<td>63.6</td>
<td>Apal, BsmI haplotypes</td>
<td>Yes ([68])</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candidate gene association study in a longitudinal cohort</td>
<td>LBP Japan</td>
<td>60 subjects</td>
<td>All females</td>
<td>Over 60 years</td>
<td>TaqI polymorphism</td>
<td>No ([67])</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Population based study</td>
<td>LBP UK</td>
<td>720 subjects</td>
<td>All females</td>
<td>53.7 ± 0.22</td>
<td>TaqI polymorphism</td>
<td>Yes ([77])</td>
<td></td>
<td></td>
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</tbody>
</table>

Association with change in Kellegren–Lawrence grade, \( p < 0.002 \). Associations of haplotypes with severity of pathology in: overall L2/3 (13 and 22, 13 and 23, \( p < 0.05 \)); young L2/3 (23 and 33, \( p < 0.05 \)); old L1/2 (11 and 13, 12 and 13, 13 and 22, 13 and 33, \( p < 0.05 \)); old L2/3 (13 and 22, 23 and 33, \( p < 0.05 \)); old L5/S (11 and 12, 11 and 23, \( p < 0.05 \)).
Osteophytes forms mostly at the margin of osteoarthritic joints or intervertebral discs. The process involved in the generation of these neoformations is unclear, probably they represent an healing response subsequent to the degeneration of the articular structures, characterized by an imbalance between hyperplasia of bone tissue and neoformation of cartilage.

In view of the importance of the vitamin D endocrine system in bone development and given the nature of osteophytes, the involvement of the VDR in the generation of these pathological features of cartilaginous tissues is possible.

In Table 4 are reported the collected studies on the association between VDR polymorphisms or haplotypes and osteophytes development in OA and LDD; BsmI and TaqI polymorphisms appeared the most involved. Regarding OA, it was reported an association of BbT haplotype with knee OA, largely explained by the presence of osteophytes rather than JSN which might indicate involvement of the VDR in the molecular mechanisms regulating the development of osteophytes [29]. The same group reported that both COL2A1 and VDR influenced separate radiological features of OA, with the COL2A1 genotype associated with JSN, thought to be due to degeneration of cartilage, while the VDR genotype associated with osteophytes. Moreover, carriers of risk alleles at both loci have a further increased risk for OA, suggesting that the definition of haplotypes of both loci might help in improving risk stratification for OA based on radiographic analysis [30].

Concerning the Apal and TaqI polymorphisms, Solovieva et al. [38] reported that in patients with hand OA, the VDR a allele carriers were associated with a tendency of lowered risks of osteoarthritis and that the AaT allele genotype appeared to pose a remarkably lower risk of osteophyte compared with the AAaT haplotype.

In contrast, it was reported no association between osteophytes or JSN and the TaqI and BsmI polymorphisms in subjects with knee OA [37] or hand and knee OA [32].

For what concern spine OA, an association between both birthweight and VDR B allele with the presence of lumbar spine osteophytes was revealed in men. Increasing osteophyte severity was significantly associated with age, adult weight, manual social class, low birthweight and lower weight at 1 year [35].

TaqI polymorphism of the VDR was found to be associated with osteoporosis of the lumbar spine in UK [77], Australia [73] and Finland [74], but not in Japan [67]. A more common and severe osteoporosis was observed in the tt than in the Tt and TT subjects, without association with severity of DSN [73]; on the contrary, a lower prevalence of osteophytes in the L4–S1 region was reported in men with the tt and TT genotypes compared with those with the TT genotype [74].

Finally, no association was revealed between osteophytes and FokI polymorphisms in Japanese subjects with LBP [69].

1.4. Vitamin D status in OA and spinal degenerative disease

1,25(OH)2D is the vitamin D active metabolite that binds most strongly the VDR [1], but the measurement of its serum concentrations is difficult because it is highly lipophilic and unstable, circulates at picomolar concentrations and presents cross-reactivity with antibodies to other vitamin D metabolites [85]. Instead, serum 25(OH)D (either 25(OH)D3 or 25(OH)D2, or both) is the most frequently reported index and the best indicator of vitamin D status in epidemiological studies, since it directly reflects the vitamin D stores, as a results of the intake from both dietary and environmental sources [86,87].

Many studies reported the association between vitamin D status and various OA and spinal diseases development and progression. In this context, it could be interesting to evaluate if vitamin D status is associated with adverse health outcomes in the presence of particular variants of vitamin D-related genes or if individuals with particular vitamin D-related genotypes may require different health recommendations, in order to optimize their vitamin D status.

McGrath and colleagues [88] launched the proposal to better establish which particular genetic variants underlie 25(OH)D status. In particular, these authors aimed to understand how common SNPs in definite genes may influence vitamin D status, dividing candidate genes into those related to the upstream production, downstream activation and subsequent elimination of the active hormone. However, these authors concluded that further research is required in order to clarify the genetic architecture of 25(OH)D concentrations, and to unravel the mechanisms of action responsible for these associations.

The association of vitamin D level with knee OA is still controversial. In 2 US population studies, low serum levels of vitamin D were found to be associated with increased risk or progression of radiographic knee OA, this relationship is independent of any effect of vitamin D on BMD [89], and hip OA [90]. In the first study it was observed that low intake and serum levels of vitamin D appeared to be associated with an increased risk for progression of knee OA. Low serum levels of vitamin D also predicted loss of cartilage, as assessed by JSN and osteophyte growth [89].

The second study reported that the risk to develop JSN was increased for subjects who were in the middle and lowest tertiles for 25(OH)D compared with subjects in the highest tertile, while vitamin D levels were not associated with the development of osteophytes and changes in radiographic hip OA [90]. This finding was confirmed in another study where no significant association was found between decreased vitamin D levels and knee osteophytes after adjusting for age and BMI [91].

Results of two longitudinal studies reported by Felson et al. [92] showed that low serum levels of vitamin D were not associated with features of OA progression.

A Japanese study observed no differences in association of vitamin D level with radiographic knee OA among VDR polymorphisms FokI, Cdx2 and Apal. However, low tertile concentrations of 25(OH)D (<35.5 nmol/L) tended to be associated with knee pain when compared with the high tertile levels (>51.5 nmol/L), independently by the presence of radiographic signs of OA [41].

Consistently, a 22-year follow up Finnish study [93] found no significant association between serum 25(OH)D level and the risk of knee or hip OA. However, a statistically significant interaction was observed between season of blood draw, winter season, and serum 25(OH)D for predicting the development of knee OA [93].

Focusing on severity of knee osteoarthritis, Al-Jarallah et al. [94] reported that of 99 patients analyzed, 92.9% were 25(OH)D deficient, with a mean serum concentration of 11.4 ± 6.07 ng/mL. However, the comparison of 25(OH)D levels to radiological findings and functional assessment showed no significant association.

Heidari et al. [95] observed that the mean serum 25(OH)D in OA patients was not significantly lower than controls, considering the entire population studied. However, in subgroup analysis, the mean 25(OH)D concentration in OA patients aged <60 years was significantly lower than controls (23.8 ± 18.8 vs. 34.5 ± 29.6 ng/mL) even after adjusting for age and sex, with a greater association observed in patients aged <55 years.

In subjects from the Rotterdam Study, Bergink et al. [96] observed a mean vitamin D intake of 64 IU/d and a mean 25(OH)D level of 66 nmol/L. Progressive ROA occurred in 5.1% of the participants in the highest tertile of vitamin D intake against 12.6% in the lowest tertile, but both intake and levels of 25(OH)D were not significantly related to incident OA and, like in the studies of McAlindon et al. [89] and Lane et al. [90], adjustment for BMD did not substantially changed any risk estimate. Nevertheless, they found also that in subjects with low baseline BMD, vitamin D status seems to influence the incidence and progression of knee OA. Thus,
Table 4
Characteristics of studies analyzing the association between VDR polymorphisms and osteophytes in OA and LDD.

<table>
<thead>
<tr>
<th>Study design</th>
<th>Disease/disease related characteristics</th>
<th>Affected sites</th>
<th>Country (ethnicity)</th>
<th>Population</th>
<th>Males/females</th>
<th>Age (males/females)</th>
<th>Type(s) of polymorphism(s)/Haplotypes</th>
<th>Association</th>
<th>Study (Ref.)</th>
<th>OR; 95%CI; p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective, population-based cohort study</td>
<td>OA</td>
<td>Knee</td>
<td>The Netherlands</td>
<td>846 elderly</td>
<td>405/441</td>
<td>68.6 ± 6.9/68.5 ± 6.8</td>
<td>TaqI haplotype</td>
<td>Yes</td>
<td>[29]</td>
<td>baT haplotype associated with increased risk of osteophytes (OR = 1.63, 95%CI = 1.09–2.45)</td>
</tr>
<tr>
<td>Random population-based study</td>
<td>Spinal degenerative disease</td>
<td>Spine</td>
<td>Australia</td>
<td>282 subjects</td>
<td>110/172</td>
<td>69.3 ± 6.4/69.6 ± 6.4</td>
<td>BsmI polymorphism</td>
<td>Yes</td>
<td>[73]</td>
<td>Presence of osteophyosis: OR TT vs Tt = 0.47, 95%CI = 0.19–1.16; severity of osteophytes: OR TT vs Tt = 0.41, 95%CI = 0.17–0.97</td>
</tr>
<tr>
<td>Population-based twin cohort study</td>
<td>Spinal degeneration</td>
<td>Lumbar spine</td>
<td>Finland</td>
<td>71 pairs (142 subjects)</td>
<td>All men</td>
<td>48.9 ± 8.1 (35–69)</td>
<td>TaqI polymorphism</td>
<td>Yes</td>
<td>[74]</td>
<td>L4–S1 region: prevalence of osteophytes 7.5% and 3.3% lower in men with Tt and Tt compared to TT genotype (p &lt; 0.001)</td>
</tr>
<tr>
<td>Population based, multigenerational cohort study</td>
<td>OA</td>
<td>Hand, knee</td>
<td>USA</td>
<td>Linkage study 1477 (hand), 1228 (knee); Association study 283 (hand), 312 (knee)</td>
<td>47% males</td>
<td>Linkage study 57.6 ± 10.8 (hand), 60.9 ± 12.1 (knee); Association study 59.7 ± 10.2 (hand), 72.6 ± 5.3 (knee)</td>
<td>Rsml polymorphism</td>
<td>No</td>
<td>[32]</td>
<td>–</td>
</tr>
<tr>
<td>Population based study</td>
<td>LBP</td>
<td>Spine</td>
<td>Japan</td>
<td>60 subjects</td>
<td>All females</td>
<td>Over 60 years</td>
<td>TaqI polymorphism</td>
<td>No</td>
<td>[67]</td>
<td>–</td>
</tr>
<tr>
<td>Population based study</td>
<td>OA</td>
<td>Knee</td>
<td>UK</td>
<td>280 cases, 469 controls</td>
<td>All females</td>
<td>66.90 cases, 63.67 controls</td>
<td>TaqI polymorphism</td>
<td>No</td>
<td>[37]</td>
<td>Subjects with BB genotype were significantly more likely to have severe osteophyte scores (p = 0.03)</td>
</tr>
<tr>
<td>Population study</td>
<td>OA</td>
<td>Lumbar spine</td>
<td>UK</td>
<td>392 Subjects (291 analyzed for VDR allelic variation)</td>
<td>219/173</td>
<td>66.0 ± 3.2/65.6 ± 2.7</td>
<td>BsmI polymorphism</td>
<td>Yes</td>
<td>[35]</td>
<td>–</td>
</tr>
<tr>
<td>Candidate gene association study in a longitudinal cohort</td>
<td>LDD</td>
<td>Spine</td>
<td>UK</td>
<td>720 subjects</td>
<td>All females</td>
<td>53.7 ± 0.22</td>
<td>TaqI polymorphism</td>
<td>Yes</td>
<td>[77]</td>
<td>Association with change in Kellegren–Lawrence grade, p &lt; 0.002</td>
</tr>
<tr>
<td>Population based study</td>
<td>OA</td>
<td>Hand</td>
<td>Finland</td>
<td>160 OA subjects, 383 non OA subjects</td>
<td>All females</td>
<td>56.3 ± 4.7 OA subjects, 53.0 ± 5.2 non OA subjects</td>
<td>Apal, TaqI polymorphisms</td>
<td>Yes</td>
<td>[38]</td>
<td>Association of a allele with lower risk of osteophytes (OR = 0.51, 95%CI = 0.25–1.03); association of AaTt genotype with lower risk of osteophytes (OR = 0.26, 95%CI = 0.08–0.91) compared with AA TT genotype</td>
</tr>
<tr>
<td>Case/control study</td>
<td>LBP</td>
<td>Spine</td>
<td>Japan</td>
<td>387 elderly (Group A, 217 = osteophyte formation with disc height narrowing, Group B, 99 = osteophyte formation without disc height narrowing, Group C, 71 = cases without osteophyte formation)</td>
<td>153/234</td>
<td>Group A 68.9 ± 6.2, Group B 67.8 ± 6.2, Group C 65.3 ± 6.6</td>
<td>FokI polymorphism</td>
<td>No</td>
<td>[69]</td>
<td>–</td>
</tr>
</tbody>
</table>
they suggested that improving the vitamin D status in the elderly could protect against the development and worsening of knee OA, especially in subjects with low BMD.

In a study concerning osteoporotic fractures in men, Chaganti et al. [97] observed that men with radiographic hip OA had a lower vitamin D level, and a higher prevalence of vitamin D insufficiency and deficiency compared with controls. Higher 25(OH)D levels were associated with a lower prevalence of radiographic hip OA after adjusting for age, season, and clinic site. Men with vitamin D insufficiency (levels of 25(OH)D 15.1–30 ng/mL) had a 2-fold increased likelihood of prevalent radiographic hip OA compared with vitamin D-sufficient men. In men with vitamin D deficiency, there was a tendency toward an increased likelihood of radiographic hip OA.

Vitamin D deficiency was common in elderly patients with symptomatic lumbar spinal canal stenosis, Lee et al. [98] observed a 55.6% of subjects with hypovitaminosis D. Stoker et al. [99] revealed a high prevalence of vitamin D abnormality, inadequacy or deficiency, in their population of subjects before undergoing spinal fusion. Also Kim et al. [100] registered pre- and post-operative levels of 25(OH)D, mean preoperative level was 15.8 ng/mL (range, 5.2–29.4 ng/mL) and increased to 19.5 ng/mL (range, 6.3–47.7 ng/mL) at 1 year after surgery, with a significant increase noted only in the deficient group. Post-operatively, there were 18 patients in the deficient group, 8 patients in the insufficient group and 5 patients in the normal group. However, vitamin D status was improved after decompressive surgery. Post-operative 25(OH)D level was significantly correlated with surgical outcomes, with the post-operative deficient group showing significantly worse surgical outcomes than those in the other groups.

In Table 5 are reported the studies analyzing the association between vitamin D status and OA or LDD.

2. Discussion

The association of VDR polymorphisms with degeneration in cartilaginous and disc's non mineralized connective tissues, evidenced in different studies, suggests that the VDR has a role in the regulation of chondrocytes metabolism.

VDR is expressed in many types of cells and tissues, including articular chondrocytes [101,102], nucleus pulposus (NP) and annulus fibrosus (AF) cells of the intervertebral disc (IVD) [80,81]. In vitro, vitamin D active metabolites have been shown to be involved in cartilage metabolism: the VDR binds to the active form of vitamin D, it helps to control the calcium balance, it may act in the differentiation, proliferation, maturation of chondrocytes [79,103] and it influences the proteoglycans synthesis [104]. Vitamin D is also involved in osteochondral regulation, participating in cartilage mineralization and endochondral ossification [105–107]. Moreover, vitamin D status modulates plasma sulfate concentrations and, thus, it may influence the amount of inorganic sulfate available for intracellular sulfation of proteoglycans [108].

Concerning IVD, vitamin D active metabolites regulate proliferation, matrix genes expression and specific cytokines and proteins production of NP and AF cells [80,81].

Thus, biologic differential interactions of these cells with the vitamin D metabolites may be critical for a healthy cartilaginous tissue and alterations in vitamin D regulated signaling pathways could have a role in the pathophysiology of the chondral degeneration.

From a clinical point of view, while peripheral joint OA and spinal degenerative disease share a number of pathological features, the extent to which the genetic determinants of these disease processes are similar is not known.

In a systematic review of genetic association studies published up until the end of 2006, Ryder et al. [109] retrieved and reviewed all the studies that have been published about the association of specific genes, OA and spinal degenerative disease and they found a number of significant associations that have been replicated within a joint category by two or more independent studies, but they suggested that sample sizes and selection (population stratification effects) may have an impact on the different observed results.

In this review, analyzing papers published up until April 2012 about the association between VDR polymorphisms, vitamin D status and cartilaginous tissue pathologies, we also found controversial reports, but the usefulness of our work resided in collecting the different data about this topic, trying to suggest particular links between different aspects of the subject. In Fig. 1 are summarized our conclusions.

At first, we tried to identify researches in which VDR polymorphisms could be associated with the development of osteochondral diseases. Despite the different results, half of the reported studies about OA and 10 out of 16 papers about LDD showed an association with VDR polymorphisms and the evaluated pathologies.

The most controversial collected results are about the association with OA. In 3 of the reported case/control studies it was found an association between TaqI and FokI and knee OA in a UK population, and between BsmI and hip OA in Italian population, while this was not reported in other 4 studies performed in UK, Belgium and Japan. The same inconsistency was observed for population based studies. An association between B*4051 haplotype (Dutch population) and Apal (UK population), BsmI (UK population) and Apal (Finland population) and knee, spine and hand OA, respectively, was observed, while it was not confirmed in other 2 studies conducted in USA and UK with patients suffering of hand and knee OA.

For what concern LDD, case/control studies suggested an association with TaqI, FokI and Apal polymorphisms in Chinese, Brazilian and Turkish population, not confirmed for TaqI and FokI in Finnish, Japanese and Norwegian ones. Almost all the collected population-based studies reported an association of TaqI, FokI, BsmI and Apal with LDD in Australian, Finnish, Japanese and English populations, not confirmed for TaqI only in one work in Japanese population.

Further, we evaluated the hypothesis that specific characteristics of those diseases, in particular, the formation of osteophytes, could be considered in the light of a differential regulation of bone and cartilage metabolism in pathological process. Six of the 10 collected works showed an association between the presence of osteophytes and VDR polymorphisms in LD. In this context, a peculiar interplay between bone and cartilaginous tissue was already suggested, considering an inverse relationship between osteoporosis and OA, with the involvement of VDR polymorphisms in both diseases [110]. It was proposed that OA is associated with underlying abnormalities in bone structure and mineralization, independently by body weight and skeletal loading [111]. The increase in bone density observed in OA indicates that the condition might initially be a subchondral bone disorder rather than a defect in cartilage, with an increase in subchondral stiffness [112], a less deformable subchondral bone with impaired shock absorbing capacity, resulting in more force being transmitted to overlying tissue, thereby predisposing to articular cartilage loss.

Finally, the influence of vitamin D status on OA and LDD was evaluated, trying to evidence if there are reports which analyzed the relation between the presence of particular genetic variants in the VDR and vitamin D levels or if a particular vitamin D status could predispose to the development or progression of such diseases. No studies were reported about LDD, while the only report collected about OA suggested no relation between the presence of particular VDR polymorphisms, vitamin D levels and signs of knee OA. In general, no association was showed between OA and vitamin D status, hypovitaminosis D only occurs, as expected, in elderly population or in patients with progressive degenerative disease.
Table 5
Characteristics of studies analyzing the association between vitamin D status and OA or LDD.

<table>
<thead>
<tr>
<th>Study design</th>
<th>Follow-up time</th>
<th>Disease/disease related characteristics</th>
<th>Country (ethnicity)</th>
<th>Population</th>
<th>Males/females</th>
<th>Age (males/females)</th>
<th>Association with vitamin D status</th>
<th>Study (Ref.)</th>
<th>OR; 95%CI; p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective observational study</td>
<td>Clinical evaluation at examinations (1983–1985 and 1992–1993); assessment of 25(OH)D (1987–1989)</td>
<td>Knee OA</td>
<td>USA</td>
<td>556 subjects</td>
<td>n.d.</td>
<td>70.3 ± 4.5</td>
<td>Yes</td>
<td>[89]</td>
<td>Vitamin D low intake (lower compared with upper tertile, OR = 4.0, 95%CI = 1.4–11.6, p = 0.009) and serum levels (lower compared with upper tertile, OR = 2.9, 95%CI = 1.0–8.2, p = 0.05) associated with an increased risk for OA progression. Low vitamin D serum levels associated with JSN (OR = 2.3, 95%CI = 0.9–5.5) and osteophyte growth (OR = 3.1, 95%CI = 1.3–7.5) associated with an increased risk for OA progression. Low vitamin D serum levels associated with JSN (OR = 2.3, 95%CI = 0.9–5.5) and osteophyte growth (OR = 3.1, 95%CI = 1.3–7.5)</td>
</tr>
<tr>
<td>Longitudinal study</td>
<td>Clinical evaluation at baseline, follow-up after a mean of 8 years; assessment of 25(OH)D at baseline</td>
<td>Hip OA</td>
<td>USA</td>
<td>237 subjects</td>
<td>All elderly women</td>
<td>≥65</td>
<td>Yes</td>
<td>[90]</td>
<td>Increased risk of JSN for subjects in the middle (OR = 3.21, 95%CI = 1.06–9.68) and lowest (OR = 3.34, 95%CI = 1.13–9.86) tertiles for 25(OH)D compared with subjects in the highest tertile</td>
</tr>
<tr>
<td>Matched and unmatched case-control study</td>
<td>Clinical evaluation and assessment of 25(OH)D at baseline</td>
<td>Knee OA</td>
<td>Australia</td>
<td>1644 twin pairs (266 monozygotic and 556 dizygotic)</td>
<td>All females</td>
<td>24–79</td>
<td>No</td>
<td>[91]</td>
<td>–</td>
</tr>
<tr>
<td>Large population-based cohort study of the elderly</td>
<td>Clinical evaluation at baseline, follow-up after a mean of 6.5 years; assessment of 25(OH)D at baseline</td>
<td>Knee OA</td>
<td>The Netherlands</td>
<td>1248 subjects</td>
<td>Rotterdam study</td>
<td>520/728</td>
<td>≥55</td>
<td>No</td>
<td>[96]</td>
</tr>
</tbody>
</table>
### Table 5 (Continued)

<table>
<thead>
<tr>
<th>Study design</th>
<th>Follow-up time</th>
<th>Disease/disease related characteristics</th>
<th>Country (ethnicity)</th>
<th>Population</th>
<th>Males/ females</th>
<th>Age (males/ females)</th>
<th>Association with vitamin D status</th>
<th>Study (Ref.)</th>
<th>OR; 95%CI; p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cross-sectional study</td>
<td>Clinical evaluation at baseline, follow-up after a mean of 4.6 years; assessment of 25(OH)D at baseline</td>
<td>Hip OA</td>
<td>USA</td>
<td>1104 elderly</td>
<td>All males</td>
<td>77.2 ± 5.3</td>
<td>Yes [97]</td>
<td>Higher 25(OH)D levels associated with a lower prevalence of OA (OR = 1.39, 95%CI = 1.11–1.74). Men with vitamin D insufficiency and deficiency had increased risk of OA (OR = 2.19, 95%CI = 1.21–3.97) and OR = 1.99, 95%CI = 0.83–4.74)</td>
<td></td>
</tr>
<tr>
<td>Cross-sectional study using a large-scale population</td>
<td>Clinical evaluation at a median of 6 months from the first visit; assessment of 25(OH)D at the first visit</td>
<td>Knee OA</td>
<td>UK</td>
<td>787 subjects</td>
<td>399/388</td>
<td>65.6 ± 2.7</td>
<td>No [41]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cross-sectional case/control study</td>
<td>Clinical evaluation and assessment of 25(OH)D at baseline</td>
<td>Knee OA</td>
<td>Iran</td>
<td>148 cases/150 controls</td>
<td>n.d.</td>
<td>60.2 ± 12.9 cases/60.1 ± 10.2 controls</td>
<td>Yes [95]</td>
<td>25(OH)D concentration in OA patients aged &lt;60 years lower than controls (OR = 2.26, 95%CI = 1.15–4.4), greater association observed in patients aged &lt;55 years (OR = 2.63, 95%CI = 1.16–5.95)</td>
<td></td>
</tr>
<tr>
<td>22-year follow-up study</td>
<td>Clinical evaluation at baseline, follow-up after 20–30 years; assessment of 25(OH)D at baseline</td>
<td>Knee and hip OA</td>
<td>Finland</td>
<td>805 subjects</td>
<td>360/445</td>
<td>380 subjects (30–39 years), 276 subjects (40–59 years), 149 subjects (&gt;50 years)</td>
<td>Yes [93]</td>
<td>Interaction between winter season and serum 25(OH)D for predicting the development of knee OA (OR = 1.57, 95%CI = 1.10–2.27)</td>
<td></td>
</tr>
<tr>
<td>Cross-sectional study</td>
<td>Clinical evaluation and assessment of 25(OH)D at baseline</td>
<td>Primary Knee OA</td>
<td>Kuwait</td>
<td>99 patients</td>
<td>9/90</td>
<td>56.5 ± 9.1 (36–80)</td>
<td>No [94]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohort study</td>
<td>Clinical evaluation and assessment of 25(OH)D at baseline</td>
<td>Lumbar spinal stenosis</td>
<td>Korea</td>
<td>106 patients</td>
<td>Postmenopausal females</td>
<td>65.53 ± 8.37</td>
<td>Yes [98]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prospective cohort study</td>
<td>Clinical evaluation and assessment of 25(OH)D before and 1 year post-surgery</td>
<td>Lumbar spinal stenosis</td>
<td>Korea</td>
<td>31 patients who underwent decompression and instrumented posterolateral fusion</td>
<td>All females</td>
<td>67.7 (54–76) deficient group; 64.0 (53–73) insufficient group</td>
<td>Yes [100]</td>
<td>Increased 25(OH)D levels 1 year after surgery in the deficient group (p = 0.017). Post-operative 25(OH)D level correlated with the changes in ODI scores (r = −0.580, p = 0.001) and in EQ-SD index scores (r = 0.379, p = 0.035) in the deficient group and with ODI scores (r = −0.665, p &lt; 0.001) and EQ-SD index scores (r = 0.601, p &lt; 0.001) in all the groups</td>
<td></td>
</tr>
<tr>
<td>Retrospective investigation of cross-sectional data</td>
<td>Clinical evaluation and assessment of 25(OH)D at baseline</td>
<td>Spinal fusion</td>
<td>USA</td>
<td>313 adults underwent spinal fusion</td>
<td>137/176</td>
<td>55.2 ± 13.1</td>
<td>Yes [99]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
OA, therefore suggesting vitamin D supplementation as therapeutic procedure in this population. Hypovitaminosis D was also observed in patients with LSS or degenerative disc pathologies, but no comparisons with matched controls were performed in these studies. Nevertheless, since vitamin D could have a role on musculoskeletal coordination and skeletal tone, after definitive surgery for LSS [98], and postoperative 25(OH)D level was significantly correlated with surgical outcomes after spinal fusion [100], the authors suggested a screening for hypovitaminosis D and sufficient supplementation with vitamin D to ameliorate the postoperative outcome.

In general, none of the collected studies reported a specific mechanism of action altered by the presence of particular SNPs in VDR in the chondrogenic tissue and, to our knowledge, no functional studies on selected cell types were performed to evaluate the putative signaling pathways involving alterations in VDR and influencing OA and LDD development and/or progression.

Nevertheless, there are different kinds of evidences, reaching the same general conclusions, about the involvement of vitamin D in the regulation of the immune system, inflammation and bone metabolic parameters in OA.

One of the reported issue in these field is the fact that epidemiological studies can only evaluate the effect of vitamin D in certain stages of the disease. In this context it was analyzed on a rat model whether vitamin D has an influence on the onset or progression of OA. The authors showed that vitamin D has a protective effect on condyle wideness during the induction of OA, despite an increase in the expression of the inflammatory and cartilage remodeling mediators MMP-3, IL-1β and TNF-α linked to the TRL-4 pathway, but a downregulation of these mediators during disease progression, without beneficial effects on the disease outcome. They concluded that vitamin D deficiency is greatly associated with the early stages of OA, suggesting vitamin D supplementation before cartilage damage occurs [113].

The effects of the presence of SNPs in VDR or inflammatory and chondrolytic mediators was also evaluated in a case (total hip arthroplasty failure)-control study to define if the individual responses to such stimuli may be influenced by genetic variations. The authors reported an involvement of a SNPs in MMP1 and VDR in aseptic failure and in osteolysis owing to deep infection, respectively [114].

Another study confirmed the effects of 1,25(OH)2D3 on matrix metalloproteases production by human articular chondrocytes in vitro. Chondrocytes within OA cartilage express VDR and MMPs 1, 3 and 9, particularly at sites of tissue degradation and 1,25(OH)2D3 has more pronounced effects on chondrocytes in states of activation and proliferation, where it appears to modulate MMPs and PGE2 production [115].

Finally, concerning the bone and cartilage crosstalk, it is to note that development and progression of OA has been associated with altered mineral-ion homeostasis and chondrocytes hypertrophy. In this context there were provided evidences that Pi and 1,25(OH)2D3 activate ERK1/2 through FGF23 signaling and are implicated in hypertrophy and impaired mineralization in late-stage OA chondrocytes [116].

In conclusion, since there are many evidences about the linkage of cartilaginous tissue pathologies and VDR genetic variants and, given the role of vitamin D in the metabolism of this tissue, it could be interesting to perform functional studies focusing on the interplay between the different gene variants and its ligand.

An interesting field of genetic associations to explore for future studies could be also the interplay of vitamin D related genes and inflammatory related genes, taking into account the specific ethnic backgrounds of patients and controls.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jsbmb.2013.03.001.

References


