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Original Research Article

Will it be possible to prevent lumbar degenerative disc diseases in the future by means of vitamin D receptor gene manipulation?

Numan Karaarslan[1*], Yasin Emre KAYA[2], Ibrahim YILMAZ[3], Hanefi OZBEK[4], Betul EKIZ BILIR[5], Necati KAPLAN[6], Duygu YASAR SIRIN[7], Yener AKYUVA[8], Mehmet Sabri GURBUZ[9], Kadir OZNAM[10], Semih AKKAYA[11], Cagri Ata MUTLU[12], Olcay GULER[13], Ozkan ATES[14] and Mahir MAHIROGULLARI[15]

[1]Assist. Prof. M.D., Namik Kemal University School of Medicine, Department of Neurosurgery, 59100, Tekirdag, Turkey.
[2]Assist. Prof. M.D., Abant Izzet Baysal University School of Medicine, Department of Orthoaedic and Traumatology, 14000, Bolu, Turkey

[3]Medical Pharmacologist; pharmacist, Istanbul Medipol University School of Medicine, Department of Medical Pharmacology, 34810, Istanbul, Turkey

[4]Prof. M.D., Ph.D; Istanbul Medipol University School of Medicine, Department of Medical Pharmacology, 34810, Istanbul, Turkey

[5]M.D., Republic of Turkey, Ministry of Health, State Hospital, Department of Endocrinology, 59100, Tekirdag, Turkey

[6]Assist. Prof. M.D., Istanbul Rumeli University, Reyap Corlu Hospital, Department of Neurosurgery, 59680, Tekirdag, Turkey

[7]Assist. Prof. Ph.D.; Namik Kemal University, Faculty of Sciences and Arts, Department of Molecular Biology and Genetics, 59100, Tekirdag, Turkey

[8]M.D., Gaziosmanpasa Taksim Training and Research Hospital, Department of Neurosurgery, 34433, Istanbul, Turkey

[9]Assist. Prof. M.D., Istanbul Medeniyet University School of Medicine, Department of Neurosurgery, 34000, Istanbul, Turkey

[10]Assist. Prof. M.D., Department of Orthopaedic and Traumatology, Istanbul Medipol University School of Medicine, 34214, Istanbul, Turkey

[11]Assoc. Prof. M.D., Private Surgery Hospital, Department of Orthopaedic and Traumatology, 20070, Denizli, Turkey

[12]M.S., Acibadem University School of Medicine, Department of Medical Science, 34752, Istanbul, Turkey

[13]Assoc. Prof. M.D., Bahcelievler Medicalpark Hospital, Department of Orthopaedic and Traumatology, 34180, Istanbul, Turkey

[14]Prof. M.D., Esenyurt University, Department of Neurosurgery, Esencan Hospital, 34517, Istanbul, Turkey

[15]Prof. M.D., Memorial Health Group, Department of Orthopaedic and Traumatology, 34758, Istanbul, Turkey

***Corresponding Author's E-mail: numikara@yahoo.com**
Pbx: +9028 2250 5000
Fax: +9028 2509 9900

Abstract

It is primarily aimed to study polymorphisms in vitamin D receptor gene (VDR), which is one of the genetic factors having a role in the formation of lumbar pathologies and/or causing higher incidence of pathologic processes. Secondarily, it is aimed to create pre-data which may help professionals to administer more effective and protective interventions in this area. Without any language preference, we searched US National Library of Medicine National Institutes of Health, Embase, OVID, Cochrane Library database of clinical trials from 1989 to Mar 11 to 2017 Mar 12, and traced all the references of incorporated documents. The data were evaluated by using descriptive statistics. Results were shown as amount or frequency (%). In literature, some vitamin D receptor gene (VDR) polymorphisms have been found in relation to widespread osteochondral diseases. When VDR polymorphisms, vitamin D level and intervertebral disc pathologies have been examined, a satisfactory answer to the question whether specific pathologies could be suppressed in terms of genetics has not been found. By means of this study, it would be understood the genetic factors inhibiting physio pathological process concerning lumbar degenerative disc disease or the genetic factors playing role in identifying physio pathological process related to lumbar degenerative disc disease by defining them. Accordingly, effective and contraceptive treatment of lumbar degenerative disc disease might be ensured soon.

Key Words: Intervertebral disc degeneration, lumbar canal stenosis, lumbar disc herniation, lumbar spinal stenosis, lumbar spondylosis, lumbar spondylolisthesis, Vitamin D receptor gene polymorphism.

INTRODUCTION

People have predisposition or susceptibility to some diseases in terms of genetics since they were born. It is well known that whereas, in most cases, genetic predispositions do not cause any diseases in the organisms where immune system works well. So some genetic diseases may occur due to the weakness in the immune system (Euesden et al., 2017; Vincze and Danko, 2012).

There are some studies indicating that immune system and cell control are affected in the deficiency of vitamin D, which is in charge of working of thousands of genes influencing immune system (Alhassan et al., 2017; Kowalczyk et al., 2017).

Vitamin D performs its functions through Vitamin D receptor (VDR) (Zarei et al., 2016). In literature, it is reported that the gene polymorphisms in this receptor play a crucial role in the pathogenesis of various cancers and diseases such as type 1 diabetes, rheumatoid arthritis, systemic lupus erythematosus and multiple sclerosis. The progress of these diseases is associated with the dysfuntion of vitamin D on the immune system (Watad et al., 2016; Dambal et al., 2017; Bogdanou et al., 2017).

It is reported that the frequencies of the aforementioned diseases increase in cases of vitamin D deficiency or VDR gene polymorphisms (Tagliabue et al., 2015; Wintermeyer et al., 2016).

Many researchers have started studying genes that have roles in the formation of intervertebral disc pathologies since the results of Human Genome Project were started to be used both in pharmaceutic biotechnology and medicine (Zhao et al., 2016; Casa et al., 2016).

Vitamin D affects bone and cartilage metabolism. A change in this system may be related to pathological situations in the cartilage tissue. In literature, there are some researches about the vitamin D receptor gene (VDR) polymorphisms related to sensitivity to general osteochondral diseases. However, the results are different from each other. Although the overwhelming majority of the researches indicate that there is a relation with lumbar intervertebral disc degeneration, it is seen that findings are related with osteoarthritis also in many of them (Brennan-Speranza et al., 2017; Zhu et al., 2014; Liu et al., 2014).

The aim of this manuscript is to make an up-to-date summary. Besides, it is intended to analyze the relation between VDR polymorphisms, vitamin D status, knee cartilage, disc pathologies and different specific pathologies. In the present manuscript, it is also aimed to bring an initiative for exclusive treatments on the genetic level.

MATERIALS AND METHODS

Search strategy

The databases of the US National Library of Medicine National Institutes of Health, Embase, OVID, and the Cochrane Library, as well as the references within the retrieved articles, were searched to find all relevant biomimetic scaffolds along with IVD studies from 1989 Mar 11 to 2017 Mar 12, without any language restrictions. The following keywords were used in the search: “lumbar pathologies”; “intervertebral disc degeneration”; “lumbar disc herniation”; annulus fibrosus”; “nucleus pulposus”; “lumbar spinal stenosis”; “lumbar spondylolisthesis”; “lumbar spondylosis”; “lumbar canal stenosis”; AND/OR “vitamin D receptor gene polymorphisms”. The

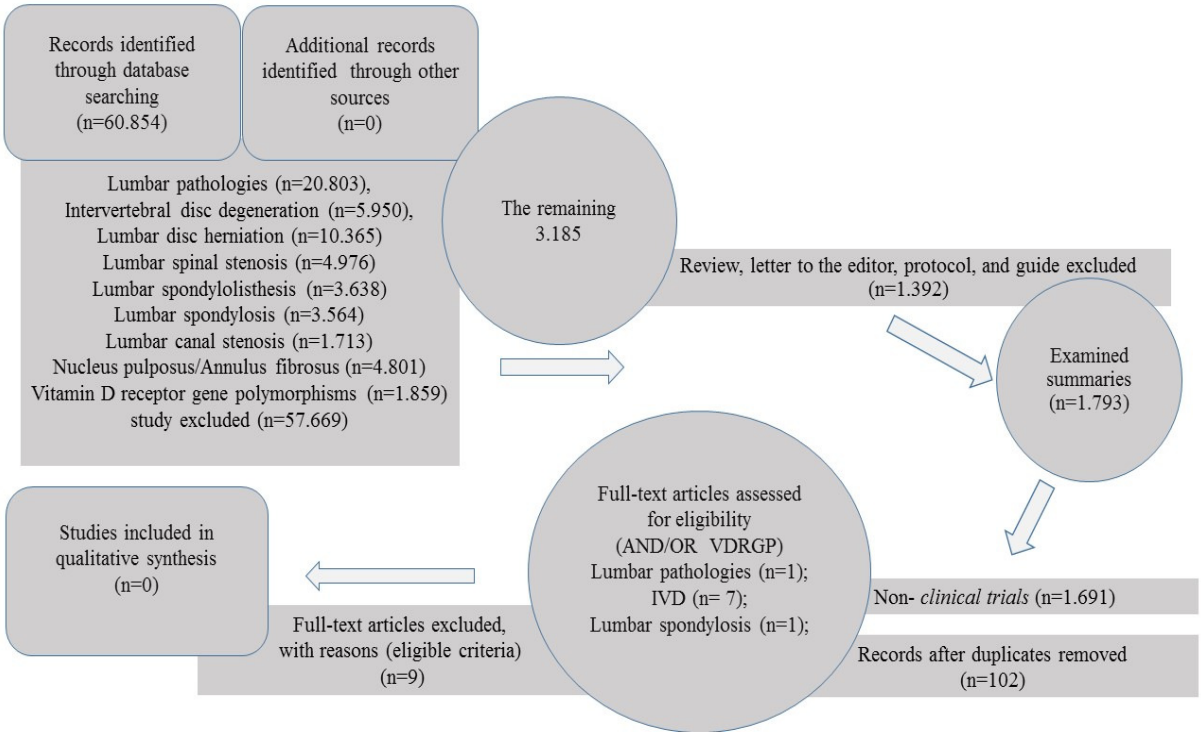

Figure 1. The follow chart of literatures identification.

percentage distribution of articles by year was recorded, and the evidence level was determined according to Lijmer et al. (Gumustas et al., 2016; Lijmer et al., 1999).

Bibliographies thought to be missed during the database research -were examined again. Unpublished grey literature, including articles, comments, letters, editorials, protocols, guides, meta-analyses, and collections, were not included. The most highly cited articles were defined and re-examined in order to avoid double entries.

Afterwards, the data obtained have been checked considering Transparent Reporting of Systematic Review (PRISMA) rules widely used in such analyses. The rationale for the review has been described in the context of what is already known in conformity with proper titles.

Eligibility criteria

It was planned to include high proof, randomized and double-blind researches pertaining to VDR and lumbar pathologies. All studies not containing the above information were excluded. The study inclusion process is summarized in *Figure 1*.

Data collection and evaluation

The authors selected the included studies independently and, in order to minimize selection bias, the studies were revised by all authors. In case of conflicting results, the final decision was taken by DYS, BEB, BB, NuKa, KO, OG, SA, and IY, who have great experience regarding pharmaco-molecular/endocrinology, orthopedic or neurosurgical device design. Finally, the senior authors (HO, OA, and MM) were consulted and the topics were revised if necessary.

Statistical analysis

We found that the obtained data had not been based upon the fact that they were collected from the sources that had probability distribution function. Therefore, non-pragmatic statistical methods were used. However, given the lack of common findings, descriptive statistical methods were applied. Microsoft Office Excel (2012) was used and the results were shown as mean ± standard deviation or frequency (%).

RESULTS

30 researches have been found related to vitamin D receptor gene and lumbar pathologies. 23 of these have been linked to vitamin D receptor gene (VDR) polymorphisms[18-40]. No clinical studies have been found (*Table 1, Figure 2*).

Table 1. Results Process.

Keywords	Manuscript (Daterange)	Manurcript (Amount)	Clinicaltrials (Amount)
Lumbar pathologies	1937-2017	21.799	996
Intervertebral disc degeneration	1942-2017	6243	293
Lumbar disc herniation	1946-2017	11.195	830
Lumbar spinal stenosis	1950-2017	5.355	379
Lumbar spondylolisthesis	1934-2017	3.855	217
Lumbar spondylosis	1946-2017	3.787	223
Lumbar canal stenosis	1950-2017	1.807	94
NP	1930-2017	3.584	66
AF	1945-2017	1.295	12
VDRGP	1989-2017	1.934	75
Lumbar pathologies AND/OR VDRGP	2017-1998	29	1
Intervertebral disc degeneration AND/OR VDRGP	2017-1998	28	7
Lumbar disc herniation AND/OR VDRGP	2006-1998	14	0
Lumbar spinal stenosis AND/OR VDRGP	2003	1	0
Lumbar spondylolisthesis AND/OR VDRGP	-	0	0
Lumbar spondylosis AND/OR VDRGP	2006-2010	2	1
Lumbar canal stenosis AND/OR VDRGP	-	0	0
Nucleus pulposus AND/OR VDRGP	2012	1	0
Annulus fibrosus AND/OR VDRGP	2012	1	0

The symbolizes are as follow: VDRGP: Vitamin D receptor gene polymorphisms, NP: Nucleus pulposus, AF: Annulus fibrosus.

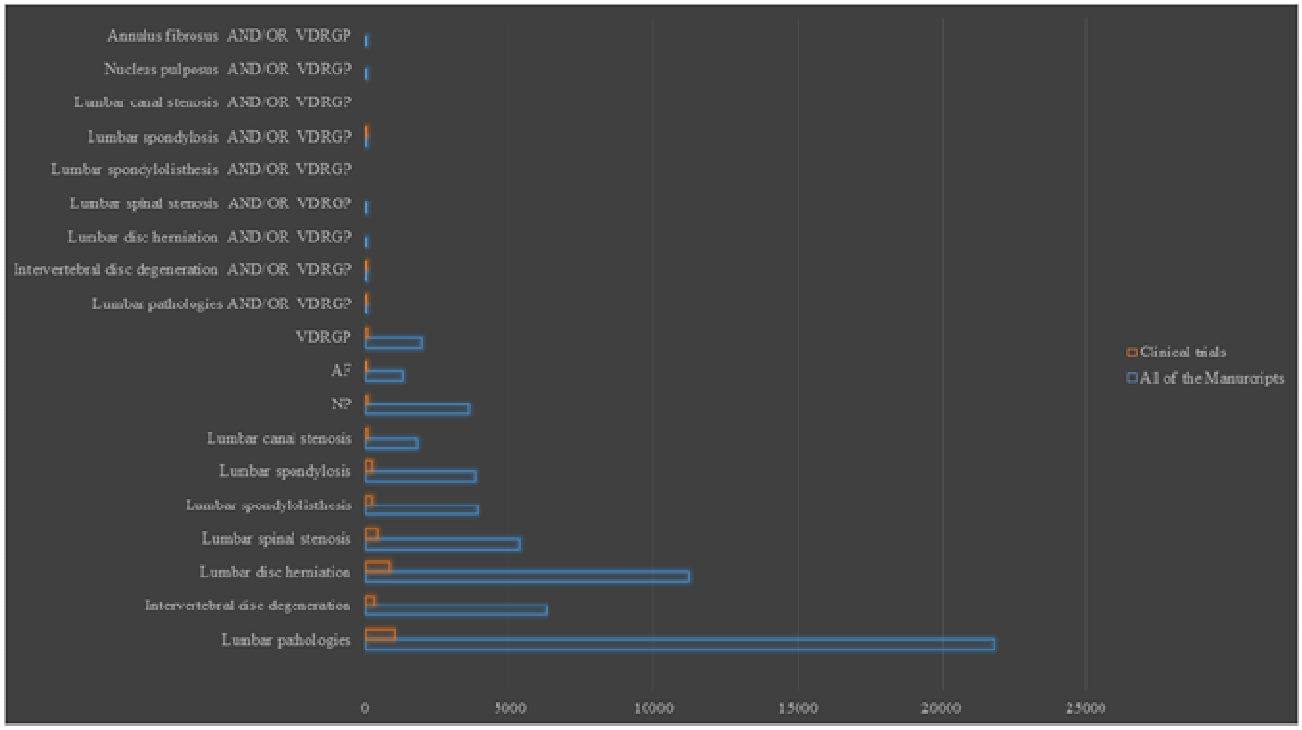

Figure 2. Distribution frequency of researches.

DISCUSSION

Until very recently it has been thought that the target organs of active vitamin D are confined to the intestine, kidney and bone. Vitamin D is not a real steroid hormone but works by means of nuclear receptors like steroid hormones.

The biological effects of vitamin D take place via genomic or non-genomic pathways. Genomic responses occur through the nuclear VD receptor. It is known that

VDR occurs in more than 30 tissues. In particular, it plays an important role in the regulation of bone cell function and maintenance of serum calcium homeostasis, which are fulfilled by active metabolites of vitamin D(Gunes et al., 2008).

Calcitriol [1,25(OH)2D3] enables calcium absorption by connecting to VDR, provides reabsorption of phosphate and adjust hormone level. VDR osteoporosis is the first gene to be determined to have an effect on bone mass(Ala-Kokko, 2002).

FokI, BsmI, ApaI and TaqI polymorphisms have been found affecting the function of the receptor regarding the association between cancer cases such as breast and colon cancers and allergic/inflammatory cases and oral problems such as periodontitis(Battie et al., 2004).

Lumbar pain is one of the major health issues in developed countries and is generally accompanied by disc degeneration. Lumbar pathologies occur as a result of many factors and result in various problems. A change in vertebral end-plate causes degeneration of the disc by affecting the aliment of the disc.

Colombini et al. (2016) carried out a study by comparing an experimental group comprised of 266 patients diagnosed with lumbar vertebra pathology with the control group comprised of 252 asymptomatic people. They expressed that they intended to evaluate allele, genotype and haplotype frequency of BsmI, ApaI and TaqI with VDR polymorphism. Besides, they conducted a questionnaire to appraise whether the patients were exposed to risk factors. They reported that they detected polymorphism using PCR-RFLP and TaqMan SNP genotyping assay. They found BbAaTT as a risk factor in all cases and bbAATT and bbaaTT genotypes as preservers. In addition, in the cases only diagnosed with a lumbar disc hernia and all lumbar cases except spondylolisthesis and lumbar stenosis, B allele, Bb, Aa and BbAaTT genotypes were found to be risky and b allele, bb, aa and bbaaTT genotypes were found to be preservative. In the cases with osteochondrosis with/without lumbar disc hernia T allele, Aa and bbAaTT genotypes were reported to be risky whereas t allele, AA and tt genotypes to be preservative. They concluded that there is no significant cooccurrence in the cases with spinal stenosis or spondylolisthesis. They emphasized the importance of a detailed clinical evaluation in order to determine haplotype analysis and biomarkers. They signified that it contributes to describe the genetic risk factors for specific lumbar spinal diseases(Colombini et al., 2016).

Toktaş et al. (2015) reported that the results of studies indicating some gene locus related to intervertebral disc degeneration were obtained from studies carried out in north European countries. They indicated that they aimed to conduct a research in which the patients would be south European people to evaluate radiological severity of lumbar disc degeneration and the relation between gene loci. They formed the experimental group, including 75 patients diagnosed with lumbar disc degeneration. The stage of their disease was from slight to severe. The control group was formed of 25 controls. They indicated that they evaluated each lumbar intervertebral space separately and concluded a total radiological score. Besides, they analyzed single nucleotide polymorphism of the predetermined genetic sample for each participant (COL1A1 Sp1, COL9a2 Trp2, COL9a3 Trp3 and VDR TaqI). They observed that degeneration scores were significantly lower in COL1A1 Sp1, COL9a3 Trp3 and VDR TaqI mutational cases. However, they found that there is no relation between mutations of COL9a2 - Trp2 and disc degeneration. Furthermore, they reported that the disc degeneration scores were much lower in the patients with more than one mutation. They indicated that a single nucleotide polymorphism seen in COL1A1, COL9a3 and VDR genes might be related to lumbar disc degeneration in that group. Yet more they deduced that if a patient had a multi mutation, the degeneration-mutation relation would be more significant. They maintained that multiple prospective studies done in a larger group involving people from different countries could help us to find out its relation to relevant genes and environmental factors. What's more, they claimed that the relation between disc degeneration and genetic mutations could be presented clearly, which might help to sustain a more convenient planning for the people inclined to related pathologies(Toktaş et al., 2015).

Sansoni et al. (2016) examined RANKL and plasma osteoprotegerin concentration both in healthy population and patients with discogenic pathologies. They aimed to observe whether the expression of lumbar disc hernia, the most widespread epiphenomenon, along with these markers is related to vitamin D receptor gene polymorphism. The experimental group consisted of 110 patients with lumbar disc hernia (detected by MRI) and the control group consisted of 110 healthy people who were categorized according to age and gender. They reported that they excluded cases with other pathologies. They informed that they measured RANKL and osteoprotegerin by immunoassay and used t test to determine the differences between markers. They signified that they expressed the correlation statistically between marker concentrations, antropometric variables and the pathology expression. They also informed that they analyzed the correlation to vitamin D receptor genotype. Although efficient osteoprotegerin concentrations were obtained, they observed that the lower RANKL gene was transcribed and accordingly the RANKL/osteoprotegerin rate was lower in the experimental group (in the whole group or classified by gender). They expressed that RANKL and osteprotegerin concentrations were independent of body mass index and age in the case group, but the concentration of them increased with age in the control group. They indicated that lumbar disc hernia was eloquently relevant to RANKL levels and the F allele of VDR gene. However, they

emphasized that it was not known whether cartilage or bone structure degradation occur firstly in intervertebral disc degeneration. They concluded that the decrease in the bone turnover rate in relation to a specific genetic substructure might be one of the most crucial factors in lumbar disc degeneration(Sansoni et al., 2016).

He et al. (2015) expressed that vitamin D receptor gene is an important gene affecting osteoporosis development. They carried out a study with postmenopausal Chinese women .They aimed to evaluate the relationship between genetic variants, BMD (BMD) and osteoporosis. They remarked that the experimental group was composed of 482 women with postmenopausal osteoporosis, whereas the control group contained 488 healthy postmenopausal women. They indicated that they measured BMD of vertebral, femoral neck and thigh using NorlandXR-46 dual energy X-Ray absorptiometry (DEXA). They denoted that genotypes of VDR genetic variants were determined by created restriction site-PCR (CRS-PCR) and verified by means of DNA sequencing method. As a result, they found that genetic variants of VDR p.glisin(Gly), 14 Alanine (Ala), p.histidin(His) and 305 Glutanın (Gln) were statistically relevant to mineral density of the vertebra, femoral neck and thigh. They concluded that VDR p.Gly14Ala and p.His305Gln genetic variants show a high level of relation to decrease in BMD in Chinese postmenopausal women. They proposed that vitamin D receptor genetic variants might be used as a marker when evaluating risk of osteoporosis(He et al., 2015).

Colombini et al. (2014) reported that the relation between fokI polymorphism (rs2228570) in vitamin D receptor and conventional risk factors was detected in Italians, yet they added that a gender analysis hadn't been made in these studies. They included 267 patients (149=male, 118=female) with lumbar vertebra disease diagnosed by magnetic resonance imaging (MRI) and 254 people (127 male, 127 female) as the asymptomatic control group. They expressed that they evaluated whether patients were exposed to the conventional risk factors. They signified that they detected fokI polymorphism by PCR restriction fragment length polymorphism (PCR-RFLP). In male patients, they observed that there was a relation between lumbar vertebra pathologies and advanced age, excess weight, similar family history, limited in free time activities, smoking, exposure to vibration effect for a long time, heavy-duty job and sedentary job. In contrast, in the female, they observed advanced age, limited free time, excess weight and similar family history were seen as a risk factor. They found that FF genotype in both genders doubled the risk of osteochondrosis development or discopathy accompanied by disc herniation. They concluded that heterozygote Ff genotype has preservation characteristics only in females. In males, they reported that only ff genotype was preservative for discopathy and/or osteochondrosis and added that F allele doubled disc hernia, discopathy and/or osteochondrosis. They underlined the importance of determining differences of life styles of both genders, genetic substructures and exposure to environmental factors while deciding treatment approaches in spinal diseases(Colombini et al., 2014).

Martin et al. (2014) reported that congenital adrenal hyperplasia (CAH) patients whose illnesses are based on 21-hydroxylase deficiency received glucocorticoid (GC) treatment and they emphasized that this class of drugs alters bone mineral metabolism. They analyzed gene polymorphisms related to BMD and also clinical and biochemical parameters in CAH patients. They carried out their research, including CAH patients treated by GC and healthy individuals. They evaluated the bone density, bone turnover markers and antropometric parameters. They used polymerase chain reaction technique in order to determine genotypes. They reported that 192-192 genotype frequency (IGF-I) was lower in poorly controlled CAH patients than the control group. They found that FF genotype (vitamin D receptor ,VDR) was in a relation to low lumbar BMD in CAH patients and there was a significant relation among 0-0 genotype (IGF-1), high β-CrossLaps values and low total BMD. They notified that their study contributed to the identification of genetic factors that might affect treatment response in CAH patients receiving glucocorticoids(Martin et al., 2014).

Kostik et al. (2014) examined bone mineralization and metabolism change depended upon VDR polymorphism in juvenile idiopathic arthritis. They included 198 patients (82 male, 116 female) in their study. They expressed that they measured BMD using lumbar spine DXA. They used Osteocalcin, CTX, parathyroid hormone, total and ionized calcium, inorganic phosphate and total alkaline phosphatase activity to evaluate bone metabolism. They reported that they used RFLP while determining TaqI (rs731236) and Cdx2 (rs11568820) VDR polymorphisms. In low and normal BMD, they observed that there was no difference in the distribution of TaqI and Cdx2 haplotype, genotype and alleles. When compared to the children with middle or high linear growth, low linear growth children had more "TaqI VDR with T allele genotypes". They found that high linear growth children had the highest A allele genotype" (GA+AA) frequency in Cdx2 VDR. They reported that girls with TT TaqI VDR polymorphism who did not receive glucocorticoid had lower BMD-Z scores than the ones carrying C alleles. They also reported that TT TaqI genotype Tanner I girls had higher total and ionic Ca level than C allele carriers. They indicated that TT genotype presence showed a negative correlation with BMD-Z score, yet a positive correlation with LBMD frequency. They reported that boys with GG Cdx2 genotype had lower total calcium values when compared to A allele carriers. They found that CTX level was higher in teenage boys (tanner IV – V) with GG genotype. They reported that the TT genotype of TaqI and GG genotype of Cdx2 VDR was a negative factor in bone

mineralization metabolism and linear growth (Kostik et al. 2014).

Kurt et al. (2012) indicated that in their design, oestrogen receptor alpha (ERa) and vitamin D receptor genes played a significant role in BMD decrease present in osteoporosis. They examined the roles of ERα PvuII/XbaI and VDR FokI/TaqI polymorphisms in BMD in Turkish postmenopausal women. They included 81 osteoporotic and 122 osteopenic postmenopausal women. They used PCR-restriction fragment length polymorphism techniques to determine the polymorphisms. They measured lumbar vertebra and BMD in the thigh using Dual-energy X-ray absorptiometry. They found similar results in the distribution of ERα and VDR genotypes. Although the whole osteoporosis prevalence was not related to these genotypes, reduced femur neck BMD value was higher in patients with ERα PvuII "PP" and ERα XbaI "XX" than the patients with "Pp/pp" and "xx" genotypes. Furthermore, they found that BMD in femur neck and total thigh was lower in VDR FokI “FF” genotype patients than “Ff” genotype patients. They emphasized that they confirmed the relation between VDR FokI “FF” genotype and the risk of fall of femur neck mineral density under 0,8 by Logistic regression analysis. They concluded that the data in their study could contribute to the determination of BMD by ERα PvuII/XbaI and VDR FokI polymorphisms in Turkish postmenopausal women(Kurt et al., 2012).

Stathopolulou et al. (2011) aimed to determine the effect of Vitamin D receptor gene polymorphism on BMD in Greek women. They carried out their research using examinatorial of healthy women (n=578). Density of lumbar vertebra and thigh bone mineral were evaluated by Lunar DPX-MD. The expressions were made by a dual-energy X-ray absorptiometry. They made genotyping for BsmI,TaqI and Cdx-2 polymorphisms in the VDR gene. When stratified by daily calcium intake, in the group with <680 mg/day intake of Ca, all studied polymorphisms had an association with lumbar spine BMD. After adjusting potential covariant, they found that BsmI and TaqI polymorphisms were related to osteoporosis development. However, they found that minor A allele presence in Cdx-2 polymorphism was related to low lumbar BMD. They stated that there is no significant difference between polymorphism genotypes in the group with high calcium intake (>680 mg/day). They emphasized that VDR gene affected BMD in the patients with low calcium intake and this effect was masked in patients with high calcium intake. As a result, they concluded that adequate calcium intake was important in postmenopausal women and had positive effect even in the patients with negative genetic susceptibility(Stathopoulou et al., 2011).

Yuan at al. (2010) aimed to find out the synergic connection between MMP-3, VDR gene polymorphisms and occupational hazard risk factors in intervertebral disc degeneration. They included 178 patients with intervertebral disc degeneration and 284 patients as the control group. They made a survey and used polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) technology. They expressed that they used additive model in order to analyze synergy between gene polymorphism and occupational hazard risk factors. They concluded that hunch/twirling, whole body vibration, heavy workload, presence of 5A allele in MMP-3 (6A5A/5A5A) and A allele presence in VDR-Apa are directly effective in intervertebral disc degeneration by non-conditional logistic regression analysis.

They indicated that there were synergic effects between MMP-3, as a mutation in 5A genotype, and whole body vibration and hunch/twirling movements. They also maintained that there is another synergic effect between VDR-Apa, as a mutation in A allele and whole body vibration exposure in terms of the formation of intervertebral disc degeneration(Yuan et al., 2010).

Eser et al. (2010) aimed to find the relation between VDR and aggrecan genes polymorphisms and degenerative disc disease. They indicated that aggrecan and VDR proteins were the main components of bone and cartilage tissues. They examined 300 patients with disc degeneration and herniation to evaluate the effects of VDR and aggrecan genes polymorphisms. They found that while TT, Tt, FF and Ff genotypes were related to disc herniation in protrusion shape, but tt and ff genotypes are related to disc herniation in extrusion/sequestration shape. Moreover, they identified an association between disc degeneration severity and some VDR gene polymorphisms (TT and FF genotypes with mild degeneration; tt, ff and Ff genotypes with severe degeneration). Also aggrecan allele types were in association with protrusion type disc herniation. They concluded that VDR and aggrecan gene polymorphism were in a relation with disc degeneration and herniation(Eser et al., 2010).

Tantawy et al. (2008), emphasized that low bone mass is a kind of bone disease seen in patients with thalassemia. They indicated that they aimed to determine calcium state and BMD in an adolescent group of transfusion dependent thalassemia. They used DXA scanning to determine femur neck and lumbar vertebral BMD in 40 patients with Beta thalassemia major. They found that the BMD values were associated with calcium, phosphorus, alkaline phosphatase, bone specific alkaline phosphatase, intact parathormone, 25-OH vitamin D levels and vitamin D receptor gene polymorphism in exon 2 (Fok1). They reported that BMD was lower in the lumbar vertebra than femur neck. They emphasized that serum ferritin level and VDR genotype had only effect on BMD in femur neck and maintained that there might be some different factors determining BMD between two areas. They indicated that the calcium level was low at 75% of the patients and 72.5 % of the patients had hypoparathyroidism. They suggested that low calcium level might be caused by hypoparathyroidism and

osteomalacia association. They remarked that sufficient iron chelation, calcium and vitamin D intake are important in order to optimized BMD in this patient group (Tantawy et al., 2008).

Koshizuka et al. (2006) carried out a study, including Japanese postmenopausal women in order to examine the relation between restriction fragment length polymorphisms (RFLPs) in oestrogen receptor (ER), vitamin D receptor (VDR), parathyroid hormone (PTH) and interleukin-1 beta(IL-1 beta) genes and radiologic severity of lumbar spondylosis which is seen from L1/2 to L5/S1.They found that ER and VDR RFLP haplotypes affected the upper spines more than the lower ones. They indicated that while VDR genotype is more effective in the older group, ER genotype is more active in the younger group. They maintained that PTH and IL1-beta polymorphisms were not related to disease severity on any level. From this point of view they concluded that ER and VDR genes might result in lumbar spondylosis in a dissimilar way, oestrogen sensitivity in the early menopause period might have a more pronounced effect on the severity of the disease, vitamin D was more important in elderly when the spondylosis effect of oestrogen deficiency was lower (Koshizuka et al., 2006).

Jordan et al. (2005) aimed to examine risk factors regarding birth weight and vitamin D receptor gene polymorphism, which is thought to play an important role in adult lumbar vertebra osteoarthritis. They scaled lumbar vertebra graphs according to disc space narrowing (DSN) osteophyte severity and collected demographic data. They obtained weights at birth and 1-year-old from records. They expressed that they analyzed alllele variations of VDR genes in 291 individuals. The mean age was 65.8 and the mean weight of women was 68.9, whereas it was 80.1 for men. They found that osteophyte level was >/=2 in 63.5 % and DSN >/=2 was found in 14.3 %. They deduced that increasing osteophyte severity was related to age, adulthood weight and social class, yet DNS was not related to these. They reported that the presence and severity of osteophyte in men were related to birth weight and low weight at the age of 1. They added that this relation was not statistically significant in women. They expressed that there were no relationship between these weights and DSN. They indicated that B allele in VDR gene was related to increased osteophyte severity. They concluded that there was a significant relation between VDR gene and birth weight while determining osteophyte risk in men. They added that this relation was similar in women, but it was not statistically significant. They concluded that both birth weight and VDR gene polymorphisms were associated to vertebra osteophyte presence and there was a significant relation between these two factors in men (Jordan et al., 2005).

Vidal et al. (2003) analyzed G□A polymorphism on the tip of 3´ in VDR gene and T□C transition in the starting codon using BsmI and FokI endonuclease in Maltese postmenopausal women. Their BMD was examined. They found that gene frequency for VDR starting codon polymorphism were CC:60.4%, CT:30.7% and TT:8.9%. Also, it was GG:16.4%, GA:51.9%, AA:31.7 for 3´ polymorphism. Both lumbar and femoral BMD were found the highest in CC homozygous in FokI genotype and GG homozygous in BsmI genotype in postmenopausal women. They concluded that there is no evidence indicating that there is a linkage disequilibrium between two alleles (Vidal et al., 2003).

Oishi et al. (2003) studied physical and structural factors affecting disc degeneration, BMD in the vertebra and osteophyte formation in the lumbar vertebra in elderly postmenopausal women. They invited 126 women who were over the age of 60. 80 of these women were studied in terms of their examination, radiography, MRI and DXA data. TaqI polymorphism of vitamin D was detected in 60 individuals. Osteophyte presence (radiographies) was found to be 61%, whereas disc degeneration (in MRI) was 68%. They indicated that body weight and body mass index was prominently correlated with anteroposterior (AP) and lateral (LAT) BMD. They found that mean osteophyte area and body weight were proportional with the number of osteophytic discs. However, they stated that these were not proportional with disc area and/or degenerated disc number. After stepwise regression analysis, they found that bodyweight and LAT-BMD values were independently related to area of osteophytes. Disc area [(r=0.386) for AP plane] and osteophyte area (r=0.384 for AP plane) were significantly associated with BMD. However, they informed that disc area and osteophyte area were not correlated with each other. They found the degenerated disc rate in the lower lumbar discs was high, but the osteophyte disc area was not so. They did not find any relation between the frequencies of T and t alleles in VDR and disc degeneration, osteophyte formation and osteoporosis. They concluded that the increase in BMD and osteophyte formation in lumbar vertebra was triggered by weight gain and body mass index, yet this increase was not correlated with disc area and there was an inverse proportion between disc area and BMD (Oishi et al., 2003).

Nakamura et al. (2001) reported that they determined a polymorphism, which forms CC, CT or TT genotype at the position 1377 in calcitonin receptor gene. They studied 152 healthy Japanese women between 16-43 ages in terms of the relationship between CTR gene polymorphisms and their BMD, height, body weight and osteocalcin levels. They reported that CTR genotype frequencies were 77.0% for CC, 20.4% for CT and 2.6% for TT. They did not find any significant difference between three genotypes in terms of height, BMD and osteocalcin levels. They indicated that height-adjusted-weight was significantly different in TT, CT and CC genotypes. In combined analyses of VDR genotype (B, b) and CTR genotype (C, T), they found that there was a

significant difference in body height between CCB and others. In addition, to analyze difference between two races in terms of CTR genotypic frequency, 64 blood samples were taken from Japanese and 47 blood samples were taken from Caucasians. A significant difference was detected in CTR genotype frequencies. They reported that C allele was predominant in Japanese, yet C and T were almost similar in Caucasians. As a result, they concluded that CTR allele was one of the genetic factors regulating body weight in Japanese women (Nakamura et al., 2001).

Langdahl et al. (2000) emphasized that vitamin D is necessary in normal bone metabolism. In early studies, vitamin D receptor gene polymorphisms of exon 2 and 9 and intron 8 were related to bone mass and bone turnover. They examined 192 osteoporotic patients and 207 individuals as the control group. They separately and totally examined the effects of these three polymorphisms on BMD, bone turnover and osteoporotic fracture prevalence. They determined 4 polymorphisms using Fok I (T2-C), Bsm I (intron8), Apa I (intron 8) and Taq I (T1055-C) by RFLP. They reported that there was no relation between Fok I polymorphism and bone mass, bone turnover and osteoporotic fracture prevalence. They found that patients with the osteoporotic fracture had more BB +Bb- genotype frequencies. In addition, they observed that the individuals with bb genotype had higher BMD in intertrochanteric area and the whole thigh. They did not find any difference in terms of Apa I and Taq I polymorphisms between osteoporotic and control group. They did not observe any difference in mineral density of lumbar vertebra, femur neck, trochanter and Wards triangle, yet mineral density in the intertrochanteric area in individuals with TT genotype was found to be higher than the individuals with Tt and tt genotype. They emphasized that the combining of genotypes reflected differences caused by Bsm I polymorphism. They concluded that translation starting polymorphism of VDR did not affect BMD and there was no relation to osteoporotic fractures in men and women (Langdahl et al., 2000).

Duncan et al. (1999) studied roles of 23 candidate genes controlling BMD. They included 115 probands (35 men, 80 women) and 499 of their first and second degree relatives (233 men, 276 women). They indicated that they measured BMD in vertebra and femur neck by dual-energy X-Ray absorbsiometer and expressed age and gender matched Z score, which was corrected according to body mass index. They reported that they studied the following candidate genes: androgen receptor, type I collagen A1 (COLIA1), COLIA2, COLIIA1, vitamin D receptor (VDR), colony-stimulating factor 1, calcium-sensing receptor, epidermal growth factor (EGF), oestrogen receptor 1 (ESR1), fibrillin type 1, insulin-like growth factor 1, interleukin-1 alpha (IL-1alpha), interleukin-4 (IL-4), interleukin-6 (IL-6), interleukin-11 (IL-11), osteopontin, parathyroid hormone (PTH), PTH-related peptide, PTH receptor type 1 (PTHR1), transforming growth factor-beta 1, and tumor necrosis factors alpha and beta. They researched the relation of 44 microsatellite in or nearby these genes with BMD. They underlined that there was a suggestive linkage between BMD and PTHR1 by MapMaker/Sibs program. They detected that there was a moderate relation with EGF, COLIA1, COLIIA1/VDR , ESR1 , IL-1alpha , IL-4 , IL-6 and BMD. They stated that they found connection in/around IL-1alpha, PTHR1, IL-6, and COLIIA1/VDR genes in the Variance components analysis, which was made by ACT program. They stated that the genes that are responsible and mutations could be verified in the light of these data (Duncan et al., 1999).

Lucotte et al. (1999) examined the relation between BMD and T/C polymorphism seen in the first of two starting codons in VDR gene. They indicated that they determined this polymorphism using a FokI restriction enzyme. They expressed that the presence of F allele indicates the absence of the first codon, whereas f allele presence indicates the presence of the first codon. They reported that they studied FokI genotype in 124 postmenopausal French women with osteoporosis, who are between 45 and 90 ages. They did not observe a significant difference in the distribution of FokI genotype between women with osteoporosis and the women in the control group. They did not find any difference in FokI expression after categorizing the cases in terms of age, the past time after menopause, weight, height, mineral density in vertebra and femur neck. However, when they examined cases under 75 years old (98 cases), they found that BMD in the femur neck area was relatively lower in cases with ff genotype (10% of the cases) than the cases with FF and Ff genotype. From this point of view, they concluded that ff genotype-VDR gene related to low BMD in the femur neck in French postmenopausal women (Lucotte et al., 1999).

After reviewing the studies that have been carried out so far, molecular defects contributing to disc degeneration have been determined in genetics studies. Vitamin D receptor, differences in tandem repetitions in aggrecan gene and some unique genetic relations including Type IX collagen gene mutations and matrix metalloproteinase 3 gene have been found (Takahashi et al., 2001).

In conclusion, many researchers agree in this idea that lumbar degenerative disc diseases, as the largest part of lumbar pain, occur as a result of mutual interaction of genetic and environmental factors due to physical stress. In the literature, it hasn't been found a satisfactory answer to the question whether specific pathologies in terms of genetics may be related to VDR polymorphisms, the status of vitamin D and data regarding lumbar pathologies. There are some controversial reports regarding the relation between VDR polymorphisms and the degeneration of intervertebral disc tissue. Moreover, in some of the researches, genetic factors have been associated with lumbar disc

degeneration, but in others not.

It is crystal clear that more experimental and clinical researches are needed in order to present this complicated pathogenesis. Current approaches to disc degeneration are surgical and conservative and they are on the side of preventing disc movement, so this results in inability in disc functions. Instead, in the future, cell based pharmacogenomics researches will be more popular and be among promising studies.

CONCLUSION

In the future, thanks to the identification of genetic factors preventing lumbar degenerative intervertebral disc pathologies or causing their formation on a high rate, doctors will be able to provide more effective and protective treatments.

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