International Journal of Environmental Sciences
ISSN: 2229-7359
Vol. 11 No. 4s, 2025
https://www.theaspd.com/ijes.php

The Effect Of Vitamin D SNP Taqi (Rs731236) On Axil Spondylarthritis Disease In Patient On Biology Treatment

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Abstract
In Axil spondylarthritis (AxSpA) disease was found increased in the level of tumour necrosis factor that produced mainly from immune cell like T cell and B cell where found in many study that tumour necrosis factor (TNF) play a major role in AxSpA development leading to increased disease activity even that take biological treatment like infliximab that supposed be TNF blocked, That where leading to another cases related to genetic type, SNP TaqI was found have effect on disease activity in patient with these SNP. Objectives: The vitamin D receptor (VDR) modulates the expression of different genes that are involved in various cell processes. Abnormality in expression and genetic polymorphism of VDR are related to Axil spondylarthritis disease (AxSpA) . also, the effect on the biological treatment (infliximab) that patients take it. Therefore, we investigated the association between the genetic polymorphism of VDR TaqI and infliximab treatment in AxSpA. Patients , Materials and methods: The study design is cross sectional study .The genotyping of VDR (TaqI) polymorphism was performed using PCR-RFLP in 150 AxSpA patients included male (108) and female (42) on biological treatment for at least 3 months, where this study done in Rheumatology Clinics of Baghdad Hospital, Medical City, Baghdad- Iraq with ethical approval from Department of Biochemistry, College of Medicine, Baghdad University. Result: SNP found in this study have relationship with disease activity in patient with these TaqI SNP , where found in this study significant relationship between Taq genotype and disease stage variant show statistical significant association with active disease from different stages, 87.5% of patients with very high disease activity had TC genotype, 66.7% of patients with high disease activity had TC genotype and 73.9% of patients with low disease activity had TC genotype.

Keywords: *Axil spondylarthritis(axSpA), Spondyloarthritis (SpA), tumour necrosis factor (TNF), vitamin D receptor (VDR).*

INTRODUCTION

Axil spondylarthritis(axSpA) disease is the prototypical form of a family of diseases known as Spondyloarthritis (SpA) characterized by inflammatory processes and new bone formation , the most common symptoms is chronic back pain (inflammatory arthritis affecting primarily the sacroiliac joints [1] [2]. A diagnosis of axSpA is generally before the age of 45 years [3] , Also There are few studies conducted on the characteristics of AxSpA in the Middle East [4] . A study conducted in Qatar reported that the mean age of the patients was 25.9 years, and at diagnosis at 32.3 years. The average delay in the diagnosis was 6.4 years. The disease was most prevalent among males(Yilmaz et al., 2025)

Thus, axSpA is a potentially debilitating disease, associated with chronic pain, deformities, and reduced function and quality of life [3]. It was found that Tuomer necrosis factor (TNF) play a major role in AxSpA development that secretion from macrophages and monocytes, but also by other immune cells, eg, neutrophils, T cells, and natural killer (NK) cells, as well as non-immune

cells. The concentration of TNF in serum correlates with the severity of infection[6]. The proinflammatory cytokine, tumor necrosis factor (TNF-α) makes a great contribution to immune system regulation, being involved in cell growth and proliferation upon binding with its receptor[7]. Tumour necrosis factor alpha (TNF alpha) blockers such as infliximab (IFX) had significantly changed the course of inflammatory diseases like Spondyloarthritis (SpA) [8] However, about 30% of patients do not respond to these treatments. This lack of response may be due to an immediate non-response known as primary failure, or to a loss of response after an initial good response called secondary failure. In the case of secondary failure, immunogenicity has been incriminated. It is defined by the development of antidrug antibodies (ADAbs) [9]. Few studies have realized the possibility impacts of vitamin D receptor (VDR) gene polymorphisms on susceptibility to AxSpA; however, the results of these studies have been inconsistent[10]. This asymmetry could be due to various agents, such as little sample sizes, inadequate power to detect associations between VDR gene polymorphisms and portability to AxSpA, the study design, the ethnicity of the examine population, and the genetic context so we studied this SNP to found layout with AxSpA. The results have influence of VDR polymorphisms TaqI SNP on various rheumatic disorders promoted us to investigate these potential relationships in AxSpA [11].

PATIENTS, MATERIALS AND METHODS:

The study was conducted in human beings and statistically considered as A cross-sectional analytical study that included 150 both male (108) and female(42) participants age of them (18 <) . Patients that included in this study have axSpA and on Infliximab treatment (biology treatment). All patients were interviewed, examined and diagnosis with axSpA depend on MRI or Xray. Patients Male or female age more than (18 <) years with Rheumatoid factor (RF) or anti cyclic citrullinated peptides (anti CCP) positivity, baseline erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels. Patients must take drug (infliximab) at last for 3 months, all patients with AxSpA and on infliximab treatment were examined, diagnosed and determined stage by physicians where this study done in Rheumatology Clinics of Baghdad Hospital, Medical City, Baghdad- Iraq.

STATISTICAL ANALYSIS:

Analysis of data was carried out using the available statistical package of SPSS-24Statistical Packages for Social Sciences- version 24 .(Data were presented in simple measures of mean, standard deviation, and range (minimum maximum values). The significance of difference of different means (quantitative data) were tested using Students t-test for difference between two independent means or ANOVA test for difference among more than two independent means. Pearson correlation was calculated for the correlation between two quantitative variables with its t-test for testing the significance of correlation. Statistical significance was considered whenever the P value was equal or less than 0.05.

RESULTS

The study included 150 patient, mean±SD of age was 38.82 ± 8.88, the youngest patient was 18 yrs. old and oldest one was 62 yrs old. The mean±SD of BMI was 28.92 ± 6.45 kg/m^2. 28% of patients were females and 72% were males. Only 16% of patients had Family of SPA and 30% were smokers, as presented in table 1-1.

Table 1-1: Mean of Age , BMI, Gender, Family SPA history and Smoking

Demographic			
Age (mean ±SD) (range)		38.82 ± 8.88	18-62 (years)
BMI (mean ±SD) (range)		28.92 ± 6.45	19.93-51.27(kg/m^2)
Gender	Female	42(no.)	28.0%

No. %	Male	108(no.)	72.0%
Family of SPA N, %		24	16.0
Smoking N, %		45	30.0
	Total	150	100.0

Vitamin D receptor gene polymorphism variant showed that Taq polymorphism had 3 genotypes, CC in 22% of patients, TT in 10% of patients and TC in 68% of patients, T allele frequency was 43.3% and C allele frequency was 56.7%. Where found association between VDR polymorphism variant and disease stage, Taq genotype variant show statistically significant association with active disease from different stages, p ≤0.006 . 87.5% of patients with very high disease activity had TC genotype, 66.7% of patients with high disease activity had TC genotype and 73.9% of patients with low disease activity had TC genotype.

Patients with TC genotype had a 4.1 (odd ratio) higher risk to have very high disease activity when in TT and CC it have 0.06,0.26 (odd ratio) higher risk to inactive disease as show in table 1-2 .

Table 1-2: The association between Taq I SNP and disease stage

		Stages				Total	p-value
		inactive disease	low disease activity	high disease activity	very high activity		
Taq I	TT	6	0	6	3	15	0.006*
		50.0%	0.0%	13.3%	12.5%	10.0%	
	odd	0.06 (0.01-0.24)	/	1.64 (0.54-4.9)	1.35 (0.35-5.22)		
	p	0.001		0.3	0.65		
	CC	6	18	9	0	33	
		50.0%	26.1%	20.0%	0.0%	22.0%	
	odd	0.26 (0.11-0.74)	1.5 (0.71-3.3)	1.08 (0.45-2.59)	/		
	p	0.01	0.26	0.80			
	TC	0	51	30	21	102	
		0.0%	73.9%	66.7%	87.5%	68.0%	
	odd	/	1.6(0.82-3.3)	0.91 (0.4-1.92)	4.1(1.17-14.6)		
	p		0.15	0.81	0.02		

Also Where was found a significant (p 0.004) relationship between duration of taken infliximab that consider a inhibition for TNF and TaqI VDR as show in table 1-3.

Table 1-3: Mean ± SD duration of INF effect in Taq VDR polymorphism variant

		N	Mean ± SD	SE	p-value
Taq I	TT	15	1.70 ± 0.25	0.06	0.004
	CC	33	1.50 ± 0.21	0.03	
	TC	102	1.51 ± 0.19	0.01	

DISCUSSION:

Axial skeleton. The terminology axSpA covers both patients who have developed structural injury in the sacroiliac joints or spine visible on radiographs and patients without structural injury, defined as non-radiographic axSpA .

In this study was including 150 patients that have different stage of disease and different outcomes, so we studied the progressive of disease in different stage and multiple symptoms.

It was found mean of age was 38.82 ± 8.88 years, the youngest patient was 18 yrs. old and oldest one was 62 yrs old and according to previous research in USA was found that diagnosis of axSpA before the age of 45 years, although onset of axSpA after this age has also been described [3] but No association was observed between the age of patient at diagnOsis or the form of the disease and the presence of any of the studied TaqI SNP . In axSpA male sex is associated with greater spinal radiographic progression. On the contrary, women tend to have greater enthesitis and experience more dactylitis that agree with result where male have greatest value of disease (72%) to female (28%) in patients with axspa, various activation of immune system, mainly Th17 axis, supports a distinct sexual dimorphism since males but not females show higher frequency of IL-17A and Th17 cells[12] .Estrogen mediated impact on immune response may a Th1 profile or a Th2 profile, depending on hormone concentration. Moreover, estrogen has been proved to enhance vitamin D function that accrue and increasing the expression of VDR. This may result in a more potent anti-inflammatory response in females than male[13] .

According to the result 18% of patients have family history of axspa that leading to not a relation between history of family and disease that agree with [14] the relationship between family history of axSpA and diagnostic delay, of which none found a significant association (Ha.

Vitamin D Polymorphisms of this gene are observed across various population groups, although the prevalence of specific VDR genotypes varies among populations. Several polymorphisms, that study TaqI (rs731236), the important ones that stay unclear , with strong linkage disequilibrium have been examined. Despite having no impact on the structure of the expressed VDR protein, the single nucleotide polymorphisms potentially have a role in regulating the expression of the VDR gene[15].

Receptor gene polymorphism variant showed that Taq polymorphism had 3 genotypes, CC in 22% of patients, TT in 10% of patients and TC in 68% of patients, T allele frequency was 43.3% and C allele frequency was 56.7% where TC is common genotype in this cases and the one that show change with different stages of disease where in active was 0% , low disease activity 73.9%, high disease activity 66.7%, very high activity 87.5% where in statistical appear Where was a significant relationship between duration of taken infliximab and Taq VDR When infliximab is one of inhibition TNF , Biological impacts of TNF that cases inflammation include activation of other cells (macrophages, T-cells, B-cells), inflammatory cytokine production (IL-1, IL-6), expression of adhesion molecule (ICAM-1, E-selectin), inhibition of regulatory T-cells, matrix metalloproteinase production and induction of apoptosis .An interesting effect of vitamin D was described by Dankers[16] [17] . also it refer in (Arif et al., 2024) that adding increasing doses of 1,25(OH)2D exalt the effects of anti-TNF. Binding and neutralizing activities against soluble TNF (sTNF) are the conclusive and common mechanisms of action of anti-TNF agents. On the opposite, study have proving that these factor have additional biological effects against precursor form transmembrane TNF (tmTNF) and Fc receptor-expressing cells [19].Vitamin D show that have an anti-inflammatory effect, as do anti-TNF drugs this agreement with [20]

CONCLUSION: VDR SNP TaqI was found to relate to axil spondylarthritis disease activity that increased at different time points of anti-TNF therapy where found that TC genotype was a significant relationship between duration of taken infliximab and TaqI VDR.