

Vitamin D Receptor Polymorphism and Male Factor Infertility

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Madam

Vitamin D is a fat soluble vitamin with two components: Vitamin D3 and D2. Vitamin D3, a pro-hormone, is produced when Ultraviolet radiation strikes the skin and 7-dehydrocholesterol (7-DHC), a derivative of cholesterol, is converted to pre vitamin D3. It isomerizes to vitamin D3 non-enzymatically. This is transported to the liver and bound to carrier proteins. Here it is hydroxylated to form 25OHD3 (the main circulating form of Vitamin D3). This is then hydroxylated in the kidney to 1, 25 diOHD3 (the metabolically active form). 1, 25 diOHD3 performs all of its genomic functions by binding with the Vitamin D receptor (VDR), which

belongs to the steroid hormones nuclear receptor family. It is a transcription factor and its three domains are firstly the DNA binding domain, secondly the ligand binding domain and thirdly the hinge region connecting the two. The first binds to the DNA at specific sites (Vitamin D response elements-VDRE), whose number depends on the cell type. The ligand binding domain has 12 helices, the terminal helix helps in its interaction with the retinoid x receptor (RXR). The binding of VDR with RXR to specific sites in the genome (VDREs) activates or suppresses transcription.¹

VDR polymorphism can lead to its malfunctioning, leading to various diseases such as Crohns disease, Tuberculosis, coronary artery disease and type 2 diabetes mellitus in susceptible patients.² Polymorphism has variations in the genes coding for the receptor. VDR polymorphism is present in only 1% of the population. The five types of

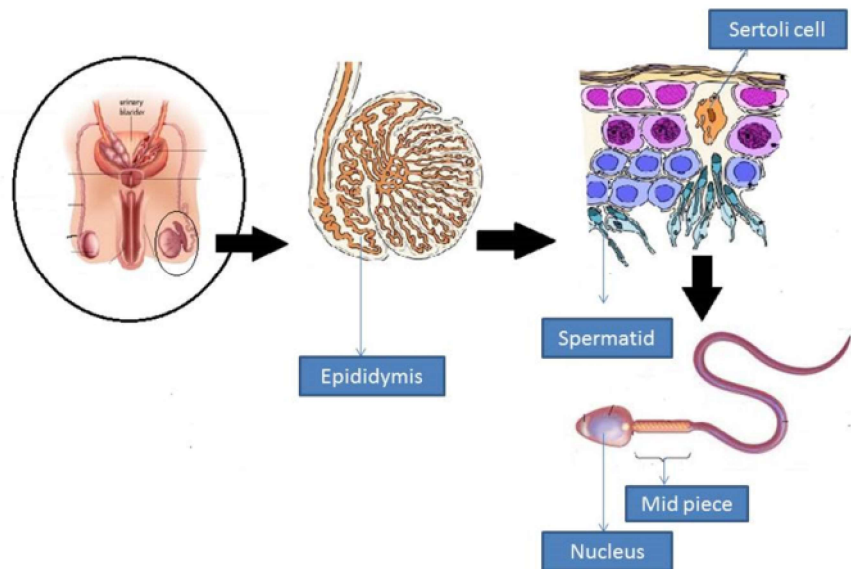


Figure: Vitamin D receptor expression in male reproductive tract.

different variations of VDR include: Apal, TaqI, FokI, and BmsI. Little is known about how these polymorphisms affect the transcription of the receptor proteins. The VDR FokI polymorphism in exon 2 causes a different site to be used for initiation of transcription. It results in three amino acids to be added to this receptor protein. However, the function role of the rest has still not been discovered.³ The male reproductive tract is one of the sites where vitamin D is metabolized. Vitamin D receptor expression in various reproductive tissues (as shown in Figure) like smooth muscles of the epididymis, spermatogonia, Sertoli cells and sperms, especially mid piece and nucleus shows that it plays a crucial role in reproduction and therefore fertility. In knockout male mice, VDR null mutant were found to have gonadal insufficiency. This included histological abnormalities of the testis, decreased sperm count and its motility.⁴ According to a study conducted in India, the FOKL VDR gene's restriction fragment length polymorphism was found to be higher in male factor infertility cases as compared to controls. Vitamin D increases sperm motility in spermatozoa by increasing

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intracellular calcium concentrations through VDR.⁵ Through the collected evidence, we conclude that Vitamin D receptor polymorphism might play a major role in male factor infertility either directly or indirectly by reducing the effects of Vitamin D. Therefore, the role of Vitamin D receptor polymorphism must be thoroughly investigated to see its role in male factor infertility cases of Pakistan.

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