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Vitamin D Receptor Interactions and Genetic Variants in the Context of Type 2 Diabetes Mellitus

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Introduction

About 90% of diabetic patients around the world have type 2 diabetes mellitus according to the World Health Organization.A significant proportion of the health care system resources worldwide are devoted to cover diagnosis, treatment and management of type 2 diabetes [1]. Moreover, it is associated with morbidity like blindness, renal failure and mortality. Type 2 diabetesis a progressive chronic disease which is marked by the inability of tissues like liver and skeletal muscles to respond to the hormone insulin which is secreted by the pancreas. Several risk factors like genetics, environmental factors and obesity contribute to the development of type 2 diabetes. Studies on genes which predispose to type 2 diabeteshave been conducted by various researchers among different ethnic populations. Genome wide association studies have led to the identification of many single nucleotide polymorphisms in certain genes and linked them to type 2 diabetes [2,3]. Recently, genes involved in vitamin D metabolism have gained interest because of the association between vitamin D deficiency and type 2 diabetes. High vitamin D levels were significantly associated with reduced risk for type 2 diabetes among Australian adult men and [4]. Vitamin D deficiency results in reduced insulin secretion in humans and rats, and its supplementation improves glucose tolerance [5]. One major study has suggested that vitamin D supplementation could lead to a significant reduction in mortality [6]. In addition, vitamin D is required for absorption of dietary calcium. Calcium is essential for insulin-mediated processes in insulin responsive tissues. Calcium repletion normalizes glucose tolerance and secretion of insulin in vitamin D-depleted rats and hypocalcemia in nondiabetics reduces insulin secretion [4].

Vitamin D and Vitamin D Receptor Interactions

Vitamin D deficiency has become an insidious epidemic among all age groups in many parts of the world. Recent discoveries have documented a protective role for vitamin D in the case of several chronic morbidities like osteoporosis, cancer, diabetes, and cardio-vascular diseases [7]. Maintaining a good vitamin D status requires adequate exposure to UV or sufficient intake from diet and supplements. Biomarkers of vitamin D status are also affected by season and geographic latitude [8]. However, variability is also attributable to genetic factors which can affect by as high as 53% [9]. Elucidations about the role of common genetic variants on vitamin D status has recently started to emanate [10]. Candidate gene studies are important to examine the effect of specific vitamin D pathway genes on other diseases and to assess the influence of genetic variation on vitamin D status.Most of what is understood about the beneficial effects of vitamin D relate to the important role of the vitamin D receptor (VDR) protein as a transcription factor, although various non-genomic actions of the VDR have also been identified. The VDR is expressed in many tissues throughout the body and modulates a variety of physiological processes, including aspects of calcium homeostasis that affect both bone formation and calcium-dependent signaling, and lipid metabolism [4-7].

Vitamin D Receptor Variants

Some of the genetic determinants for vitamin D status include the VDR gene which is particularly a good candidate for disease susceptibility, because of its involvement in insulin metabolism [11,12]. Several research studies have focused on the association between VDR genetic polymorphisms in the context of vitamin D deficiency and type 2 diabetes. Among these polymorphisms, Fok I, Taq I, Bsm I, EcoR V and Apa I are all suspected to alter the activity of the VDR protein and modulate susceptibility to type 2 diabetes. Vitamin D regulates the expression of the insulin receptor gene, and insulin secretion by binding VDR [5]. Vitamin D regulates the expression of the insulin receptor gene, and insulin secretion by binding VDR. This cytosolic/nuclear receptor acts as a transcriptional factor for many genes. VDR gene is an interesting candidate for type 2 diabetes pathogenesis and clinical manifestations. This gene is located on chromosome 12q13.1 and consists of 14 exons.VDR is expressed in many tissues involved in the regulation of glucose metabolism such as muscles and pancreatic cells. Once it binds vitamin D, it undergoes a conformational change that facilitates its binding to retinoid X forming a heterodimer which in turn interacts with the vitamin D responsive elements in the promoter region of target genes, hence modifying their expression [11-13].

Findings from a research study indicated that VDR polymorphism in exon 9 (Taq I) and intron 8 (Bsm I) were significantly associated with type 2 diabetes among Caucasian Americans from European origin [14,10]. Moreover, the metabolic parameters which characterize type 2 diabetes including dyslipidemia, hypertriglyceridemia, and low HDL levels were correlated with the reported VDR polymorphism. The results were in concordance with another research conducted in Saudi Arabia [15]. Other researchers failed to demonstrate a similar link among Indians, Turkish and Polish Populations [3,16]. This discrepancy in findings from different studies is attributed in fact to the differences in population genetics. Examining population-based genetic association between VDR variants and type 2 diabetes could of extreme importance for a specific population that has a high prevalence of both type 2 diabetes and VTD deficiency like that of the United Arab Emirates [17]. Such studies could direct future strategies for prevention and treatment of type 2 diabetesby designing new more relevant population-based interventions which can specifically and effectively target “high risk individuals”.

Conclusion

Genetics plays a complex role in the pathogenesis of both vitamin

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D deficiency and type 2 diabetes. Genome wide studies have led to the identification of several genetic variants which are associated with certain diseases like type 2 diabetes mellitus. These variants are often population-based determinants which could predispose a particular ethnicity to a certaindisease, hence significantly increasing its prevalence. The VDR primarily acts as a transcription factor–controlling the amounts of certain proteins that are produced from the DNA in the genetic code. The proteins produced by the DNA that the VDR targets are responsible for processes from inflammation to lipid storage and calcium regulation, and deficiencies in vitamin D are associated with many diseases, particularly type 2 diabetes. The VDR also has several non-DNA-related actions, but these are generally much less well understood than the genomic effects. Studies which aim to characterize the interaction of the VDR and its ligand would be informative. Model membranes which mimic the composition of sphingolipid- and cholesterol-rich microdomainsact as a model of 'normal' VDR-membrane interactions. Examining the interaction of vitamin D with such models could help identify the factors that modulate these interactions and develop a better understanding of the mechanisms of VDR-related pathogenesis in several disorders including type 2 diabetes.

The DNA sequences of the human genome have revealed that many genes are polymorphic. In coding or non-coding regions of a specific gene, there may be either a single base pair substitution of one nucleotide for another or a variable number of repeats of a short, repetitive DNA sequences. These variations may influence the rate of gene transcription, the stability of the messenger RNA or the quantity and activity of the resulting protein. Thus the susceptibility or severity of a number of disorders will be influenced by possession of specific alleles of polymorphic genes. The polymorphic many genes that have received a great deal of research interest such as PPARG2, TCF7L2, and FTO because of their association with diabetes.

References

1. WHO (2013). Factsheets. Retrieved November 5, 2013, from http://www.who.int/mediacentre/factsheets/fs312/en/index.html
2. McGrath JJ, Saha S, Burne TH, Eyles DW (2010) A systematic review of the association between common single nucleotide polymorphisms and 25-hydroxyvitamin D concentrations. J Steroid Biochem Mol Biol 121:471-477.
3. Ahn J, Yu K, Stolzenberg-Solomon R, Simon KC, McCullough ML, et al (2010) Genome-wide association study of circulating vitamin D levels. Hum Mol Genet 19:2739–2745.
4. Gagnon C, Lu ZX, Magliano DJ, Dunstan DW, Shaw JE, et al (2011) Serum 25-hydroxyvitamin D, calcium intake, and risk of type 2 diabetes after 5 years: results from a national, population-based prospective study (the Australian Diabetes Obesity and Lifestyle study). Diab Care 34: 1133–1138.
5. Kumar S, Davies M, Zakaria Y, Mawer EB, Gordon C, et al. (1994) Improvement in glucose tolerance and beta-cell function in a patient with vitamin D deficiency during treatment with vitamin D. Postgrad Med J 70: 440–443.
6. Autier P, Gandini S (2007) Vitamin D supplementation and total mortality: a meta-analysis of randomized controlled trials. Arch Intern Med 167:1730–1737.
7. Holick MF (2007) Vitamin D deficiency. N Engl J Med 357:266–281.
8. Grant WB (2009) In defense of the sun: An estimate of changes in mortality rates in the United States if mean serum 25-hydroxyvitamin D levels were raised to 45 ng/mL by solar ultraviolet-B irradiance. Dermato Endocrinol 1:207-214.
9. Shea MK, Benjamin EJ, Dupuis J, Massaro JM, Jacques PF, et al. (2009) Genetic and non-genetic correlates of vitamins K and D. Eur J Clin Nutr 63:458–464.
10. Wang TJ, Zhang F, Richards JB, Kestenbaum B, van Meurs JB, et al. (2010) Common genetic determinants of vitamin D insufficiency: a genome-wide association study. Lancet 376: 180-188.
11. Nosratabadi, R, Arababadi MK, Salehabad VA, Shamsizadeh A, Mahmoodi M, et al. (2010) Polymorphisms within exon 9 but not intron 8 of the vitamin D receptor are associated with the nephropathic complication of type-2 diabetes. Int J Immunogenet 37: 493–497.
12. Levin G, Robinson-Cohen C, De Boer I, Houston D, Lohman K, et al. (2012) Genetic Variants and Associations of 25-Hydroxyvitamin D Concentrations With Major Clinical Outcomes. JAMA 308: 1898-1905.
13. Garcia-Bailo B, El-Sohemy A, Haddad PS, Arora P, Benzaied F, et al. (2011) Vitamins D, C, and E in the prevention of type 2 diabetes mellitus: modulationof inflammation and oxidative stress. Biologics 5:7-19.
14. Speer G, Cseh K, Winkler G, Vargha P, Braun E, et al. (2001) Vitamin D and estrogen receptor gene polymorphisms in type 2 diabetes mellitus and in android type obesity. Eur JEndocrinol 144: 385-389.
15. Al-Daghri N, Al-Attas O, Alokail M,Alkharfy K, Draz H, et al. (2012) Vitamin D Receptor Gene Polymorphisms and HLA DRB1*04 Cosegregation in Saudi Type 2 Diabetes Patients. J Immunol 188: 1325-1332.
16. Bid HK, Konwar R, Aggarwal CG, Gautam S, Saxena M, et al. (2009) Vitamin D receptor (FokI, BsmI and TaqI) gene polymorphisms and type 2 diabetes mellitus: a North Indian study. Indian J Med Sci 63: 187–194.
17. Al Anouti F, Thomas J, Abdel-Wareth L, Rajah J, Grant W, et al. (2011) Vitamin D deficiency and sun avoidance among university students at Abu Dhabi, United ArabEmirates. DermatoEndocrinol 3: 235-239.