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Metabolic Syndrome and VDR Gene Polymorphism

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Abstract: ***Metabolic syndrome, which is one of the most prevelance diseases in today era. Sedentary life style surrounded by sophisticated advance technological. This leads to increase incidence of many studies which has yielded results connecting such kind of life with greater impact on many chronic diseases and low functional capability of the individuals. Metabolic syndrome (MetS) is a complex process and one of the most important groups of diseases, presenting a major health problem in developing countries like India. MetS is an increasing risk for coronary heart disease, stroke and peripheral angiopathy. MetS comprises overweight and abdominal obesity, insulin resistance or glucose intolerance (type 2 diabetes mellitus – some persons are genetically predisposed to insulin resistance), hypertriglyceridemia with low HDL and high LDL cholesterol, accompanied by arterial hypertension. The prevention of metabolic syndrome should start as early as possible. Regarding physical activity, the period of childhood and adolescence is very important from the aspects of public health.***

Keywords: Metabolic Syndrome, VDR gene polymorphism, Type2 Diabetes, Cardiovascular diseases

1. Introduction

Today, new world many changes have occurred in life of all people around. Malnutrition, unhealthy diet, smoking, alcohol consuming, drug abuse, stress and so on, are the consequences of unhealthy life style latter leads to a normal day to day life style. But every day the lives of people around faces whole lot of new challenges. For example, because new technologies such as the internet and virtual communication lead the world to a major challenge that threatens and compromises the healthy physical and mental life of the individuals.

Definition: Metabolic Syndrome (MetS) is a defined cluster of cardio metabolic abnormalities that increases an individual's risk of T2DM, Coronary Heart Disease (CHD), and cardiovascular disease (CVD). The core components of MetS are glucose intolerance or diabetes, obesity, hypertension, and dyslipidemia—specifically hyper - triglyceridemic and low levels of high - density lipoprotein cholesterol (HDL - C). Its precise definition varies slightly between guidelines issued by expert groups such as the World Health Organization (WHO), the European Group for the Study of Insulin Resistance, the National Cholesterol Education Program Third Adult Treatment Panel (NCEP ATP III) and, more recently, the International Diabetes Federation (IDF) and the American Heart Association/National Heart, Lung, and Blood Institute.

According to the new International Diabetes Federation (IDF) definition, for a person to be defined as having the MetS they must have:

Central obesity (defined as waist circumference 394cm for Europid men and 380cm for Europid women, with ethnicity specific values for other groups) plus any two of the following four factors [2]:

- Raised TG level: > 150 mg/dL (1.7 mmol/L), or specific treatment for this lipid abnormality
- Reduced HDL cholesterol: < 40 mg/dL (0.9mmol/L) in males and < 50 mg/dL (1.1 mmol/L) in females, or specific treatment for this lipid abnormality.
- Raised blood pressure: systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg, or treatment of previously diagnosed hypertension.
- Raised fasting plasma glucose (FPG) ≥ 100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes.
- If above 5.6 mmol/L or 100 mg/dL, OGTT is strongly recommended but is not necessary to define presence of the syndrome.

Vitamin D refers to a group of fat soluble secosteroids responsible for enhancing intestinal absorption of calcium, iron, magnesium, phosphate and zinc. Humans derive vitamin D from cutaneous synthesis (in the form of cholecalciferol (D3)), diet (in the form of D3), and nutritional supplements (in the form of D3) or ergocalciferol (D2). Upon exposure to UV B radiation (UVB), 7 - dehydrocholesterol in the skin is converted to pre - vitamin D3, which is immediately converted to vitamin D3 in a heat - dependent process. After ingestion or synthesis, vitamin D is hydroxylated in the liver to form 25 hydroxyvitamin D, 25 (OH) D2 or 25 (OH) D3, its major circulating form, which has little biological activity.25 (OH) D is converted in the kidney by 25 (OH) D - 1alph hydroxylase (CYP27B1), to its bioactive hormonal metabolite 1, 25 dihydroxy - vitamin D (1, 25 (OH) 2D or calcitriol). The primary action of 1, 25 (OH) 2D is through the nuclear vitamin D receptor (VDR), which heterodimerizes with the retinoid X receptor and binds to vitamin D - responsive elements near target genes. The primary action of 1, 25 (OH) 2D is to enhance intestinal calcium absorption and to promote osteoclast function, thereby maintaining calcium and phosphorus homeostasis and bone health.

However, the discovery that nearly all tissues in the body express the VDR and that several tissues also expressCYP27B1, thereby allowing for local production of 1, 25 (OH) 2D with a paracrine effect, has provided important insights into the pleiotropic effects of vitamin D and its potential role in a variety of extra - skeletal tissues, including many that affect endocrine disease. The increased appreciation of the pleiotropic effects of vitamin D and the high prevalence of hypovitaminosis D in the general healthy population, have generated very high interest in Vitamin D

among researchers, clinicians and the lay public. Vitamin D acting on its own receptors can produce a number of desired biological effects via different mechanisms and, therefore, contributes to the improvement of human health. Vitamin D has been implicated in the pathogenesis of several endocrine conditions, including primary hyperparathyroidism, type 1 diabetes (TIDM), type 2 diabetes (T2DM), autoimmune thyroid, adrenal diseases, and polycystic ovary syndrome (PCOS).

2. Incidence

The prevalence of this disorder has been increasing in recent years and stands at about 25% globally; it is therefore among the main health problems in the world. The incidence of metabolic syndrome has been reported to range from 28 persons per 1000 persons - year to more than 70 per 1000 persons - year in different regions of the world. As a result of rapid economic changes, the increased popularity of the western lifestyle and lack of physical activity, the world faces the threat of obesity and type 2 diabetes epidemics. If the current trend in obesity and type 2 diabetes continues unchanged, the incidence of metabolic syndrome will be expected to increase, especially in developing countries like India.

3. Review of Literature

The available literature reveals that functions of vitamin D are not limited to skeletal effects, and a non - skeletal action of vitamin D under active investigation is in insulin or glucose metabolism. Vitamin D status may play a significant role in glucose homeostasis as in vivo and in vitro studies have provided biological evidence of its effects on insulin secretion and sensitivity.

Allelic differences in the Vitamin D receptor (VDR) gene may contribute to the genetic predisposition to certain diseases. As Vitamin D modulates insulin secretion, it is feasible that the genetic variants of VDR gene may contribute to the development of T2DM. Two studies have reported link between VDR polymorphism and diabetes risk - one in Caucasian subjects, for BsmI site; and the other in Bangladeshi Asians, for ApaI site. Polish population showed no association between VDR FokI, ApaI, BsmI and TagI polymorphism and diabetes risk. A North Indian study also showed the same result.

However, Blumberg et al. have further defined the molecular mechanism by which unliganded VDR and calcitriol liganded VDR regulate adipogenesis. They also demonstrated that VDR is expressed early in adipogenesis. VDR were expressed sequentially at high, but short - lived, levels beginning at 30 min and lasting for only a few hours after adipogenic activation. Variations at the VDR locus have been associated with susceptibility and progression to several diseases. VDR gene polymorphisms have been linked to higher susceptibility to vitamin D deficiency in children and adolescents. The VDR TaqI allele is associated with obesity; BsmI and ApaI VDR genes are also significantly associated with overweight and obesity, and the BsmI VDR polymorphism appeared to influence body mass index (BMI).

A few studies have demonstrated that VDR polymorphisms were related to obesity, diabetes, insulin sensitivity and insulin secretion. VDR BsmI and FokI polymorphisms have been previously reported to be associated with anthropometric and biochemical parameters describing MS. Trzmiel et al. (2008) found that VDR BsmI polymorphism seemed to influence BMI, while the FokI VDR polymorphism appeared to affect insulin sensitivity and serum HDL cholesterol in men [9]. However, Lwow et al. (2008) indicated that VDR BsmI polymorphism did not seem to predispose postmenopausal women to obesity and insulin resistance, but the genotype BB was connected with dyslipidemia [10]. Frey et al. (2003) did not find evidence for the association of VDR polymorphisms with glycemia index. Results of these study seemed to be in conflict with the pleiotropic effect of the VDR gene in individuals with MetS, and this result was not found in other populations. Moreover, interactions in circulating glucose, triglyceride, cholesterol and insulin levels were not well explained. Although vitamin D deficiency is associated with an unfavourable lipid profile in cross - sectional analyses; however, Ponda et al. suggest that correcting for a deficiency might not translate into clinically meaningful changes in lipid concentrations [11].

4. Hypothesis

It is Hypothesize that the VDR gene polymorphism will give a significant result as prognostic indicator of MetS patients in the near future.

5. Objectives

To evaluate the clinical utility of VDR gene polymorphism and its association in Patients with Metabolic Syndrome (MetS). The specific research questions addressed are thus:

- What is the clinical utility of vitamin D testing in subjects with Metabolic Syndrome Disease?
- What is the frequency of vitamin D deficiency in patients with Metabolic Syndrome during the study period?

6. Approach

Study design: Analytical, Cross Sectional study.
Study population: The study will be carried out amongst the patients attending Medicine OPD hospital, Imphal, Manipur who are habituated to Manipuri food habit and life style.

Measurement for routine Blood parameters: Fasting venous blood sample will be obtained after overnight fasting and plasma Vitamin D and relevant biochemical parameters such as Glucose, total cholesterol, triglycerides, high - density lipoprotein (HDL), low density lipoprotein (LDL), will be measured.

Genotyping: DNA extraction from MetS patient collected blood sample and Genotyping of VDR gene.

7. Prevention

The best way to prevent metabolic syndrome is to maintain a healthy weight, eat a healthy diet, and be physically active, quit smoking and proper sleep, reduced anxiety and stress. More prone if family history of having diabetes. However, intervention exercise programs should not be limited to younger age groups, but must encompass all age groups within population.

8. Treatment

Habit of eating healthy food, Aim to attain the optimal BMI of the body, medication to reduce the triglyceride, BP and blood sugar level normal along with the physically active exercise.

Complication: High risk of diabetes, heart disease, stroke, or all three.

Summary: Reviewing and surveying the research article the assessment of the relationship between *VDR* gene polymorphism and the risk of Type 2Diabetes, MetS and obesity still do not give a clear answer to whether they directly impact to the metabolic disorders. So, It is still important to examine how this *VDR* gene polymorphism are related to Type 2Diabetes, obesity, and MetS in our ethinic groups.

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