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Type 2 Diabetes Mellitus: Mini Review

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Abstract – Type 2 diabetes mellitus (T2DM) is a metabolic disorder that is characterized by hyperglycemia (high blood sugar) in the context of insulin resistance and relative lack of insulin. Type 2 diabetes is caused by a combination of lifestyle and genetic factors .Some of these factor are such as diet and obesity, are under personal control while other factors such as increasing age, female gender, and genetic are beyond control. In this review we hypothesize the role of genetic polymorphism in gene Association of Rho Guanine Nucleotide Exchange Factor 11 (ARHGEF11), NOD-Like Receptor Family Pyrin Domain Containing 3 (NLRP3), Low –Density Lipoprotein Receptor-Related Protein 5 (LRP5), Toll Like Receptor 4 (TLR4) and the risk of Type 2 Diabetes Mellitus.

Keywords: Type 2 Diabetes, TLR4, ARHGEF11, LRP5, NLRP3

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1. INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) previously known as non-insulin-dependent diabetes (NIDDM)' is a complex heterogeneous group of metabolic conditions characterized by increased levels of blood glucose due to impairment in insulin action and/or insulin secretion (Das & Elbein 2006). There is an absolute lack of insulin due to breakdown of islet of beta cells in the pancreas (Shoback, 2011). The classic symptoms of diabetes are polyuria (frequent urination), polydipsia (increased thirst), polyphagia (increased hunger) and weight loss (Vijan, 2010). Other symptoms that are commonly present at diagnosis include a history of blurred vision, itchiness, peripheral neuropathy, recurrent vaginal infections, and fatigue (Shoback, 2011). It caused by a combination of genetic and environmental and behavioral risk factors (Chen, et al 2011).

2. DIAGNOSIS OF T2DM

According to (WHO, 2007) both Type 1 and Type 2 Diabetes. If the fasting plasma glucose concentration is > 7.0 mmol/L (> 126 mg/dl) or plasma glucose 2 hours after a standard glucose challenge is > 11.1 mmol/L (> 200 mg/dl). A random blood sugar of greater than 11.1 mmol/l (200 mg/dL) in association with typical symptoms (Vijan, 2010). A glycated hemoglobin (HbA1c) of ≥ 48 mmol/mol (≥ 6.5 DCCT %) is another method of diagnosing diabetes. In 2009 an International Expert Committee that included representatives of the American Diabetes Association (ADA), the International Diabetes Federation (IDF), and the European Association for the Study of Diabetes (EASD) recommended that a threshold of ≥ 48 mmol/mol (≥ 6.5 DCCT %) should be used to diagnose diabetes (IEC 2009). This recommendation was adopted by the American Diabetes Association (ADA 2010). T2D is managed with diet, exercise, oral hypoglycemic agents and sometimes exogenous insulin.

3. EPIDEMIOLOGY OF T2DM

Diabetes is common in both the developed and the developing world. It remains uncommon, however, in the underdeveloped world (Shoback , 2011). Women seem to be at a greater risk as do certain ethnic groups (Abate and Chandalia, 2001). such as South Asians, Pacific Islanders, Latinos, and Native Americans. This may be due to enhanced sensitivity to a Western lifestyle in certain ethnic groups (Carulli, et al 2005). Traditionally considered a disease of adults, type 2 diabetes is increasingly diagnosed in children in parallel with rising obesity rates (Vijan, 2010). The Rates of diabetes in 1985 were estimated at 30 million, increasing to 135 million in 1995 and 217 million in 2005 (Smyth and Heron 2006). This increase is believed to be primarily due to the global population aging, a decrease in exercise, and increasing rates of obesity (Smyth and Heron 2006). T2D is the most common form of the disease accounting for approximately 90% of all affected individuals .The highest rates of T2D are found among Native Americans, particularly the Pima Indians who reside in Arizona in the US, and in natives of the South Pacific islands, such as

Nauru (Wild et al., 2004). T2D is also known to be more predominant in Hispanic and African American populations than in Caucasians. In 2000, it is estimated that 171 million people (2.8% of the world's population) had diabetes and that by 2030 this number will be 366 million (4.4% of the world's population). The vast majority of this increase will occur in men and women aged 45 to 64 years living in developing countries. The 'top' three countries in terms of the number of T2D individuals with diabetes are India (31.7 million in 2000; 79.4 million in 2030), China (20.8 million in 2000; 42.3 million in 2030) and the US (17.7 million in 2000; 30.3 million in 2030) (Wild et al., 2004). Clearly, T2D has become an epidemic in the 21st century.

4. CAUSES OF T2DM

The development of type 2 diabetes is caused by a combination of lifestyle and genetic factors (Ripsin *et al* 2009).

4.1 Life style factor

A number of life style factors are known to be important to the development of type 2 diabetes, including obesity and being overweight (defined by a body mass index of greater than 25), lack of physical activity, poor diet, stress, and urbanization (Abdullah, et al 2010). The major environmental risk factors for T2D are obesity (> 120% ideal body weight or a body mass index > 30 k/m2) and a sedentary lifestyle (Van and Shaw 2003). The tremendous increase in the rates of T2D in recent years has been attributed, primarily, to the dramatic rise in obesity worldwide (Zimmet et al, 2001). It has been estimated that approximately 80% of all new T2D cases are due to obesity (Lean, 2000). Excess body fat is associated with 30% of cases in those of Chinese and Japanese descent, 60-80% of cases in those of European and African descent and 100% of cases in Pima Indians and Pacific Islanders (Shoback , 2011). Those who are not obese often have a high waist–hip ratio (Shoback, 2011)

Dietary factors also influence the risk of developing T2D. Consumption of sugar-sweetened drinks in excess is associated with an increased risk (Malik, et al 2010). The type of fats in the diet are also important, with saturated fats and trans fatty acids increasing the risk, and polyunsaturated and monounsaturated fat decreasing the risk (Risérus, et al 2009). Eating lots of white rice appears to also play a role in increasing risk (Hu, et al 2012). A lack of exercise is believed to cause 7% of cases (Lee, et al 2012). Persistent organic pollutants may also play a role (Lind, et al 2012).

The other major T2D risk factor is physical inactivity. In addition to controlling weight, exercise improves glucose and lipid metabolism, which decreases T2D risk. Physical activity, such as daily walking or cycling for more than 30 minutes, has been shown to significantly reduce the risk of T2D (Hu et al., 2003). Physical activity has also been inversely related to body mass index and insulin glucose tolerance test (IGT). Recently, intervention studies in China (Pan *et al*., 1997), Finland (Tuomilehto *et al*., 2001) and the US (Diabetes Prevention Program Study Group, 2002) have shown that lifestyle interventions targeting diet and exercise decreased the risk of progression from IGT to T2D by approximately 60% . In contrast, oral hypoglycemic medication only reduced the risk of progression by about 30%. A lack of sleep has been linked to type 2 diabetes. This is believed to act through its effect on metabolism (Touma and Pannain 2011). The nutritional status of a mother during fetal development may also play a role, with one proposed mechanism being that of altered DNA methylation (Christian and Stewart 2010).

4.2 Genetic factor

The major genetic risk factor for most of T2D involvemany genes with each being a small contributor to an increased probability of becoming a T2D (Shoback , 2011). Family studies have revealed that first degree relatives of individuals with T2D are about 3 times more likely to develop the disease than individuals without a positive family history of the disease (Flores et al., 2003; Hansen 2003; Gloyn 2003). It has also been shown that concordance rates for monozygotic twins, which have ranged from 60-90%, are significantly higher than those for dizygotic twins. If one identical twin has diabetes, then chance of the other developing diabetes within his lifetime is greater than 90%, while the rate for non identical siblings is 25–50% (Herder and Rode 2011). As of 2011, more than 36 genes had been found that contribute to the risk of type 2 diabetes (Herder and Roden 2011). All of these genes together still only account for 10% of the total heritable component of the disease (Shoback 2011). The Transcription Factor -7- like-2 (TCF7L2) allele, for example, increases the risk of developing diabetes by 1.5 times and is the greatest risk of the common genetic variants (Shoback 2011). Most of the genes linked to diabetes are involved in beta cell functions. It is clear that T2D has a strong genetic component. Some of the important genes associated with Type 2 diabetes are discussed below:

1. Rho Guanine Nucleotide Exchange Factor 11 (ARHGEF11) Gene

Rho Guanine Nucleotide Exchange Factor 11 is a protein that is encoded by the ARHGEF11 gene contain 41 exaon in humans and is located on chromosome no.1q21-q24 ARHGEF11 protein contains 1,522 amino acids and has molecular mass of 168.6 kD (Rumenapp et al., 1999). The C-terminal region (amino acids 1,181–1,522) of ARHGEF11

protein has been shown to regulate ARHGEF11 protein activity (Chikumi *et al.,* 2004).

ARHGEF11 is an activator of Rho GTPases that plays a fundamental role in the regulation of G protein signaling and a number of cellular processes, including insulin secretion (Hirosumi *et al* 2002; Geiger *et al* 2005; Larsen *et al* 2005) and In insulin signaling through the activation of p38 mitogen activated protein kinase and Jun NH2-terminal kinase pathways. (Nevins and Thurmond 2005; Kowluru and Veluthakal 2005) and lipid metabolism (Houssa *et al* 1999). Rho family small GTP-binding protein TC10 activation and phosphatidylinositol 3-kinase activation regulates the dynamic actin rearrangement required for insulin-stimulated translocation of GLUT4 (Khayat *et al* 2000; Chiang *et al* 2001). These data suggest that proteins involved in G protein signaling, such as ARHGEF11, may play an important role in glucose homeostasis.

Human ARHGEF11 is a member of a Rho family of guanine nucleotide exchange factors (RhoGEFs) that contain regulator of G protein signaling domains. Three closely related RhoGEFs consisting of ARHGEF1 (p115RhoGEF), ARHGEF12 (LARG) and ARHGEF11 (PDZ-RhoGEF) (Fukuhara *et al* 2001). which are involved in G protein-coupled receptor to stimulate Rho activation (Wettschureck and Offermanns 2002). In addition, Swiercz *et al* 2002) found that ARHGEF11 can be phosphorylated by tyrosine kinases and directly interact with plexin B1, a receptor for Semaphorin 4D (also known as CD100). ARHGEF11 is highly expressed in various tissues of humans, such as liver, muscle, pancreas and adipose tissue (Hirotani M, et al 2002). Therefore, the ARHGEF11 gene can be also considered as a good candidate for the etiology of T2DM and insulin resistance.

Genetic Polymorphism of ARHGEF11 Gene:

Recent studies showed that R1467H G/A variant (dbSNP ID: rs945508) in the ARHGEF11 gene with the risk of T2DM or insulin resistance. However, contrary to the findings in the Old Order Amish population (Fu *et al* 2007) the minor allele A was identified as a risk variant for T2DM in Pima Indians population (Ma *et al* 2007) and German Caucasians populations (Bottcher, *et al* 2008) and koreans population (Qing *et al* 2010), Chinese population (Jing *et al* 2011). It is well known that the inconsistency in the results of genetic variants may result from different ethnic groups and geographic regions or may be implicated in linkage disequilibrium with a true functional variant in ARHGEF11 gene. But the relationship between ARHGEF11 gene polymorphisms and the susceptibility to T2DM as well as diabetes-related metabolic traits has not been studied yet in Indian Population.

2. NOD-Like Receptor Family Pyrin Domain Containing 3 (NLRP3) Gene :

NLRP3 (NLR family, pyrin domain containing 3), also known as NALP3 or cryopyrin, is one of best-described members of nod like receptor (NLR) family (Fritz et al., 2006). It is located on the chromosome no. 1q. The Activated NLRP3 interacts with apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC), and with cysteine protease caspase-1, forming a cytoplasmic complex (NLRP3 inflammasome) (Cassel *et al*., 2009; Schroder *et al.,* 2010). This leads to activation of caspase-1 and subsequent secretion of proinflammatory cytokines such as IL-1β and IL-18 (Cassel *et al*., 2009; Schroder *et al*., 2010). NLRP3 plays a crucial role in the pathogenesis of (T2DM) (Crook, 2004;; Pickup, 2004; Masters et al., 2010; Stienstra et al., 2010; Vandanmagsar et al., 2011; Fernandez-Real and Pickup, 2012). T2DM is characterized by insulin resistance (IR) and subclinical chronic inflammation (Donath and Shoelson, 2011; Sjoholm and Nystrom, 2006). NLRP3 activation induces inflammation leading to insulin resistance (IR) and the progression of T2DM (Crook, 2004; Pickup, 2004). (GWAS) have consistently linked the NLRP3 gene to T2DM-related inflammatory markers (i.e. C-reactive protein and fibrinogen) in European people (Dehghan *et al.*, 2009, 2011).

Genetic polymorphism of NLRP3 Gene:

A recent study has provided in *vivo* evidence that NLRP3 expression is elevated in T2DM patients (Lee et al., 2013). This indicates a pivotal role of NLRP3 in the development and progression of IR and T2DM. Based on this pivotal role, and the association of variants in NLRP3 gene with NLRP3 mRNA stability and its expression (Hitomi et al., 2009; Villani et al., 2009; Zhang et al., 2011). Variant of NLRP3 gene is related to insulin resistance and increased risk of T2DM susceptibility in Chinese Han population (Yingying *et al* 2013). But the relationship between NLRP3 gene polymorphisms and the susceptibility to T2DM as well as diabetes-related metabolic traits has not been studied yet in Indian Population.

3. Low –Density Lipoprotein Receptor-Related Protein 5 (LRP5) Gene :

Low-density lipoprotein receptor-related protein 5 (LRP5) is a member of the low-density

lipoprotein receptor family which is encoded by LRP5 gene. It is located on chromosome no. 11q13. It is the co-receptor ligand of the WNT signaling pathway (Tamai *et al* 2000). WNT and insulin signaling pathways exhibit cross-talk at multiple levels and the WNT co-receptor LRP5 has a positive effect on

insulin signaling. Altered WNT and LRP5 activity can modify insulin action and insulin resistance in the patho-physiology of diabetes and metabolic syndrome (Palsgaard *et al* 2012). LRP5 was highly expressed in hepatocytes and pancreatic β cells (Kim *et al* 1998; Figueroa *et al* 2000).

In the past, many researchers have focused on the role of *LRP5* in osteoporosis (Balemans *et al* 2007; Coin *et al* 2000; van *et al* 2008). But DNA sequence analysis indicated that LRP5 is related with T1D. So LRP5 might confer susceptibility to diabetes (Hey *et al* 1998). Animal models indicated that LRP5 was required for normal cholesterol and glucose metabolism, and LRP5-deficient mice showed increased plasma cholesterol levels when fed with high-fat diet and markedly impaired glucose tolerance when fed with normal diet (Fujino *et al* 2003).

Genetic polymorphism of LRP5 Gene:

Many SNPs have been identified in human LRP5 gene and were reported to be associated with metabolic diseases, such as obesity (Guo *et al* 2006), hypercholesterolemia (Suwazono *et al* 2006) and hypertension (Suwazono *et al* 2006; Suwazono *et al* 2006). The role of LRP5 in people's susceptibility to T2DM are limited, which were conducted only in Japanese population (Zenibayashi *et al* 2008) United Kingdom populations (Guardiola *et al* 2009) and Chinese population (Xuan *et al* 2014) and their results were contradictory.

Overweight and obesity are strong risk factors for T2DM (Fujimoto *et al* 2012). The previous study reported that *LRP5* was associated with obesity (Guo *et a*l 2006). To understand the *LRP5* effect on risk of T2DM other than the effect on obesity, we compared the genotypes for patients with diabetes mellitus and controls with different BMI. No LRP5 variant was associated with T2D in Han Chinese population but haplotype TT was found to be associated with T2D (YOU H, Fei, et al 2015). But the relationship between LRP5 gene polymorphisms and the susceptibility to T2DM as well as diabetes-related metabolic traits has not been studied yet in Indian Population.

4. Toll Like Receptor 4 (TLR4) Gene:

Toll-like receptor 4 is a protein that in humans is encoded by the TLR4 gene. TLR4 gene present on the chromosome no. 9. The molecular weight of TLR 4 is approximately 95 kDa. Polymorphisms in genes that encode proteins related to the innate immune system, such as the toll-like receptors (TLRs), could influence the immune response as well as the development of T2DM (Bagarolli *et al* 2010). TLRs are evolutionary conserved Pattern-Recognition Receptors (PRRs) that play a key role in the activation of innate immune response by recognizing highly conserved pathogen-associated molecular patterns (PAMPs), such as the Lipopolysaccharide (LPS) component of gram-negative bacteria (Meylan *et al* 2006; Arancibia *et al* 2007) . Human orthologs of TLR4 are known to comprise at least 10 members (Zarember and Godowski P 2002). Each TLR family member recognizes a specific pathogen component and, upon activation, triggers a signaling cascade leading to the production of inflammatory cytokines, releasing of antimicrobial peptides, and activation of the adaptive immune response (Akira *et al* 2001; Takeda and Akira 2005) Toll-like receptor 4 (TLR4) recognizes (LPS) as a ligand (Takeda and Akira 2005) and is expressed in macrophages, airway epithelia, adipose tissue, skeletal muscle, pancreas, and vascular endothelial and smooth muscle cells (Shi *et al* 2006). It also interacts with endogenous ligands such as free-fatty acids, heat shock proteins 60 and 70, fibrinogen and fibronectin, which are elevated in T2DM patients (Shi *et al* 2006; Sasu *et al* 2001 ; Smiley *et al* 2001).

Genetic polymorphism of TLR4 Gene:

A large number of epidemical studies have reported that (TLR4) gene plays an important role in the development of T2DM. It is the most important genes influencing T2DM risk in several population. Evidence from several published studies reported that these TLR4 genetic variants were statistically significantly associated with the risk of T2DM in different population in International population (Illig *et al* 2003; Rudofsky *et al* 2004; Creely *et al* 2007; Kim *et al* 2008; Buraczynska, *et al* 2009; Maldonado *et al* 2011; Arora *et al* 2011; Jiang *et al* 2012; Fu, *et al* 2013; Cai, *et al* 2013; Zhao *et al* 2013; Lei *et al* 2014; Taís *et al* 2014; Tao *et al* 2015). But the relationship between TLR4 gene polymorphisms and the susceptibility to T2DM as well as diabetes-related metabolic traits has not been studied yet in Indian Population.

CONCLUSION

The development of Type 2 Diabetes is caused by a combination of lifestyle and genetic factors. The major genetic risk factors for most of T2DM involve many genes with each being a small contributor to an increased probability of becoming a T2DM. The ARHGEF11 gene can be considered as a good candidate for the etiology of T2DM and insulin resistance. GWAS have consistently linked the NLRP3 gene to T2DM-related inflammatory marker. Polymorphism at 10754558 and 4612666 alleles of NLRP3 gene is related to insulin resistance and increased risk of T2DM susceptibility outside the in Indian population. Many SNPs have been identified in human LRP5 and were reported to be associated with metabolic diseases, such as obesity, hypercholesterolemia and hypertension. No LRP5 variant was associated with T2DM but haplotype TT was found to be associated with T2DM outside the Indian population. Several studies reported that TLR4 genetic variants were statistically significantly associated with the risk of T2DM outside the Indian

population. Polymorphism of TLR4 gene at sites Asp299Gly and Thr399Ile, 13726TNC and 15090GNA, +986A/G, +1196C/T, +3725G/C, and +11367G/C have been found to be associated with T2DM. Studies related to the role of these genes are in the onset of T2DM are lacking in Indian population.

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