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POLYMORPHISMS OF PEROXISOME PROLIFERATOR-ACTIVATED RECEPTORS (PPARS) IN OBESITY AND TYPE 2 DIABETES MELLITUS (T2DM)

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ABSTRACT

Background: Analysis of clinical, anthropometric and genetic of T2DM is required for better therapeutic application. Analysis of PPARs and their disease susceptible and protective aspect is most important for reducing the complications of T2DM. T2DM and obesity are polygenic environmental disorders and both are highly associated with anthropometric, clinical and genetic factors in many ethnic groups. Since diet is risk factor for the disorders, identifying the genes that are regulated by the diet may give a better insight to the diagnostics and therapeutics of both, Obesity and T2DM. Genes control vital metabolic pathways and identifying gene polymorphisms may be an effective treatment but the genes associated with one population however fail to be associated with other populations. This is because of the difference in the expression frequency of disease susceptible alleles in different populations due to changes in the environmental factors. This type of different expression profile and genetic variation exit in all genes, PPAR γ/α/δ, since PPARs are linked with diet and environmental factors. Although all the polymorphisms of PPARs are associated with obesity and T2DM, this article has a broad review on Pro12Ala polymorphism of PPAR γ which is associated with

hypertension, physical activity, increased insulin clearance, lipid profile, adiposity in adults and children etc. Moreover, Ala allele carriers have protective effect against metabolic syndromes and T2DM because Ala allele is associated with high intake of oleic acid or polyunsaturated fatty acids (PUFA), high hepatic glucose uptake (GU), low body mass index (BMI), etc. In conclusion, PPARs (alpha, gamma and delta) are strongly associated in the susceptibility to obesity and T2DM with a minor protective effect of Ala allele on T2DM subjects. PPAR gamma also shows beneficial effect due to gene-diet interaction.

KEYWORDS: Polymorphisms, obesity, type 2 diabetes mellitus, lipid profile.

1. INTRODUCTION

T2DM is a polygenic environmental disorder mainly due to high caloric diet intake, high abdominal fat storage and insulin resistance. Food affects the expression of genes[1] in individuals and both diet and genes alter health of individuals because genes are regulated by diet and some diets are risk factors for diseases.[1,2] It is known fact that high LDL-C (Low Density Lipoproteins Cholesterol), high TG (Triglyceride) and low HDL-C (High Density Lipoprotein Cholesterol) are strong predictable factors for obesity, CVD (cardiovascular diseases) and T2DM.[3] Formation of H_2O_2 in peroxisomes is responsible for NEFA (Non-Esterified Fatty Acids)-induced toxicity and elevated levels of NEFAs contribute to lipotoxicity, β-cell dysfunction and β-cell loss.[4] Susceptibility to T2DM may be due to environmental[5,6] clinical[7] and genetic risk factors.[8] The phenotypes of T2DM (BMI, blood pressure, serum insulin and glucose level and plasma lipid profile), the metabolic syndromes (hyperglycemia, dyslipidemia, hypertension, hyperadiponectemia) and islet inflammation (role of immune cell mediated inflammation early in the disease pathogenesis targeting the slowing down of immune system due to loss of beta cells)[9] are also associated to the development of T2DM. Identifying genes that are regulated by diet in an individualized intervention and a β-cell Genetic Risk Score (β-GRS)[10] would be better diagnostic tools for the disorders.

2. FACTORS THAT INCREASE SUSCEPTIBILITY TO OBESITY AND T2DM

The risk factors are physical inactivity related abnormalities and clinical associated risk factors (cholesterol, triglycerides etc.) apart from genetic risk factors. Physical inactivity is linked with obesity, insulin resistance and T2DM.[11] Effects of exercise and lack of exercise provide evidence about insulin action, sensitivity and responsiveness.[12] Out of the risk factors associated with T2DM, alcohol consumption, smoking and physical inactivity–

induced insulin resistance[13] in skeletal muscle[14] play a major role in the susceptibility to T2DM and there are much differences observed in insulin secretion and sensitivity in NAFLD (Non-Alcoholic Fatty Liver Disease) in T2DM.[15] However, new alcohol drinkers in middle age and drink rarely may experience benefit in CVD and diabetic complication[16] whereas rare and light drinkers after moderately increasing alcohol consumption over short period of time are associated with lower risk of T2DM.[17] Moreover, cigarette smoking and smoking cessation lead to higher short-term risk of T2DM.[18]

Cholesterol plays an important role in membrane organization dynamics and function.[19] Visceral obesity is associated with high plasma TG and low plasma HDL-C.[20] There is a link between elevated serum cholesterol and reduced insulin secretion.[21] Moreover, the direct effect of cholesterol on β-cell metabolism may contribute in β-cell dysfunction and the onset of T2DM in obese patients.[21] Obese patients have elevated plasma cholesterol which can regulate signal transduction and gene expression through cholesterol activated transcription factors in adipocytes.[22] Excess cellular cholesterol is directly linked to reduced Glucose Stimulated Insulin Secretion (GSIS) and the normal secretion of insulin can be restored after the cholesterol depletion from the cell.[21] Therefore, regulation of cellular cholesterol may improve GSIS in pancreatic β-cell.[21]

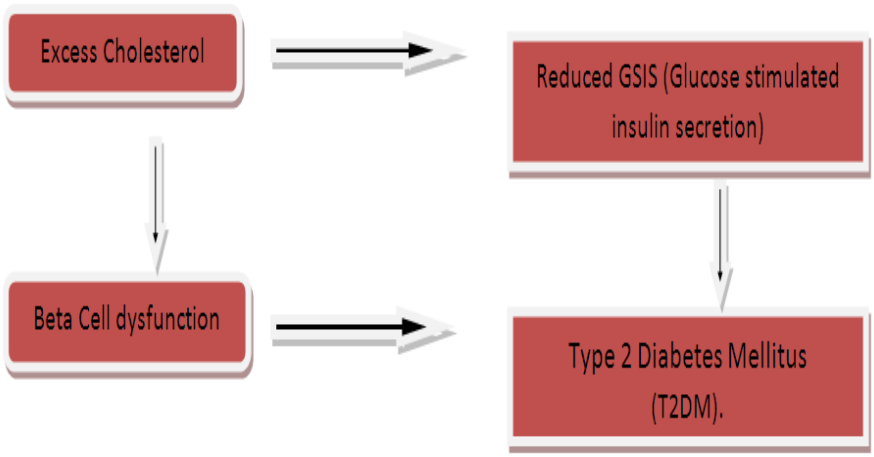

Figure 1: Role of Cholesterol to the susceptibility of T2DM.

3. PREVALENCE OF T2DM

The prevalence of diabetes in all age-groups worldwide is estimated to be 2.8% in 2000 and 4.4% in 2030. The compiled table below has two parts, diabetic projection between 2000 and 2030 and 2010 and 2030. The table has only top 10 countries which have the highest projected diabetic population in 2000, 2010 and 2030 with rank starting from 1 to 10.

Diabetic population of countries in 2010 differ from 2000 and the projection for the year 2030, table 1. In the year 2000[23], Germany and Mexico were not in the list of top 10 countries (having highest diabetic population) but in 2010 projections[24], Italy and Bangladesh were not in the list of top 10 countries (having highest diabetic population). Moreover, the diabetic population of Indonesia has declined in 2010 from 2000.

Table 1: Prevalence of diabetes predicted in 2000 and 2010 for 2030.

Projection between 2000 and 2030 People with diabetes (millions)[23]					**Projection between 2010 and 2030 People with diabetes (millions)[24]**			
Rank	Country	2000	Country	2030	Country	2010	Country	2030
1.	India	31.7	India	79.4	India	50.8	India	87.0
2.	China	20.8	China	42.3	China	43.2	China	62.6
3.	U.S.A	17.7	U.S.A	30.3	U.S.A	26.8	U.S.A	36.0
4.	Indonesia	8.4	Indonesia	21.3	Russian Federation	9.6	Pakistan	13.8
5.	Japan	6.8	Pakistan	13.9	Brazil	7.6	Brazil	12.7
6.	Pakistan	5.2	Brazil	11.3	Germany	7.5	Indonesia	12.0
7.	Brazil	4.6	Bangladesh	11.1	Pakistan	7.1	Mexico	11.9
8.	Russian Federation	4.6	Japan	8.9	Japan	7.1	Bangladesh	10.4
9.	Italy	4.3	Philippines	7.8	Indonesia	7.0	Russian Federation	10.3
10.	Bangladesh	3.2	Egypt	6.7	Mexico	6.8	Egypt	8.6

Diabetes prevalence is very high in India, age group between 20 to 40 years[25] and all over the world ([26], projection for the year 2035) and is also evident from the various means of deaths[27], therefore, a genetic analysis of the problem is very important and urgent.

4. PEROXISOME PROLIFERATOR-ACTIVATED RECEPTORS (PPARs)

PPARs are super-family nuclear receptors associated with normal and disease related processes such as lipid metabolism, inflammation etc.[28] The isoforms of PPARs are PPAR alpha (α), PPAR delta (δ) and PPAR gamma (γ). Evident suggests that PPAR-α/δ/γ polymorphisms may contribute to the risk of hypertriglyceridemia independently or in an interactive manner.[29] The above table 2 gives a brief summary of study of different polymorphisms of PPARs in different ethnic groups.

Table 2: Polymorphisms of PPARs in different ethnic groups with different disorders.

Population	Gene	Polymorphism	Specificity of Study	Disorder /Metabolic Syndrome	Reference
Japanese men	PPAR γ2	Pro12Ala	Effect on Adiposity and insulin sensitivity		(Mori *et al.*, 1998)
Caucasian	PPAR γ2	Pro12Ala	Association	Obesity	(Beamer *et al.*, 1998)
Korean	PPAR γ2	Pro12Ala	Significance of Mutation		(Oh *et al.*, 2000)
Caucasian	PPAR γ2	Pro12Ala	Insulin Sensitivity	Glucose Tolerance	(Ek *et al.*, 2001)
Japanese and + Americans	PPAR γ2		Differential effect	T2DM	(Nemoto *et al.*, 2002)
Male Caucasian	PPAR γ2	Pro12Ala	Association (Cholesterol and Low Density Lipoproteins	T2DM	(Zietz *et al.*, 2002)
Finnish	PPAR γ2	Pro12Ala	Association study with body weight change	T2DM	(Lindi *et al.*, 2002)
Polish	PPAR γ2	Pro12Ala		T2DM	(Malecki *et al.*, 2003)
Japanese men	PPAR γ2	Pro12Ala	Low adiponectin		(Takata *et al.*, 2004).
Hispanic, Non-Hispanic White women	PPAR α	C161-- >T	Association	Insulin Resistance	(Moffett *et al.*, 2005)
African American and whites	PPAR γ2	Pro12Ala	Inverse effect	Adiposity	(Fornage *et al.*, 2005)
Chinese Han	PPAR γ2	Pro12Ala	Association	Myocardial Infection	(Li *et al.*, 2006)
Chinese Women	PPAR α		Association (Lipid & dietary polyunsaturated fatty acid).		(Chan *et al.*, 2006)
Non-Hispanic Whites	PPAR γ		Association with Physical activity	T2DM	(Nelson *et al.*, 2007).
Chinese	PPAR γ2	Pro12Ala	Association	Hypertension	(Lu *et al.*, 2008)
Spanish Mediterranean	PPAR α & PGC-1	L162V & G482S	Association with alcohol consumption		(Francès F, 2008)
African-Americans	PPAR α		Association (apolipoprotein and triglyceride)		(Shin *et al.*, 2008)
Danes	PPAR γ2	Pro12Ala	Prospective study	ACS	(Vogel *et al.*, 2009)
Palestinian	PPAR γ2	Pro12Ala	Effect on Metabolic and Clinical Characteristics	T2DM	(Ereqat S, 2009).
Tunisian	PPAR γ2	Pro12Ala	Gender-Specific effect	Obesity	(Ben Ali et al., 2009)
Brazilian	PPAR α		Association (serum lipid)		(Chen *et al.*, 2010)

Chinese	PPAR γ2	Pro12Ala	Association with lipid and lipoproteins		(Chang-Quan *et al.*, 2011).
Iranian	PPAR γ2	Pro12Ala	Relation to Pioglitazone	Insulin Resistance	(Namvaran *et al.*, 2011)
Greek Children	PPAR γ2	Pro12Ala	Age-dependent and diet-modified	Obesity	(Dedoussis *et al.*,2011).
Chinese	PPAR δ & γ		Gene-Gene interaction	Obesity	(Ding *et al.*, 2012)
Chinese Han	PPAR α/δ/γ		Gene-Gene interaction	Hypertriglyceridemia	(Gu *et al.*, 2013)
Brazilian	PPAR α &γ2			Nonalcoholic fatty liver disease	(Domenici *et al.*, 2013)
Indian	PPAR γ		Role	T2DM	(Arup Kumar Pattanayak, 2014)
Chinese Han	PPAR α & γ		As risk factors	Dyslipidemia	(Shu-Jun Gu, 2014).

4.1 Allele frequency of PPARs

The distribution of genotypes of PPARs is different in different ethnic groups, diseased and controls and sexes, men and women. However, separate analysis by gender reveals that obese men have significantly higher frequency of Pro/Ala genotypes compared to controls but not in women subjects. Ala allele is significantly more frequent in males than in females.[30] The Ala allele frequencies are distributed according to a latitudinal trend (In Europe, Ala allele frequency is highest in the northern and central European populations and lowest is in the Mediterranean populations). Environment may have influenced the difference in distribution of the Ala allele in Europe. Considering the world populations, a significant inverse relationship between Ala allele frequency and T2DM prevalence is observed due to changes in the environmental factors and dietary habits which may interfere with genes.[31] The frequency of the Pro12Ala polymorphism in the Polish population studied is similar to that in other Caucasian populations.[32] Ala allele frequency is lowest in patients with both T2DM and hypertension, followed by patients with either T2DM or hypertension and highest in subjects without these conditions.[33] The frequency of the V allele of the L162V polymorphism of PPAR α is four times higher in men than women.[34] This confirms that different ethnic groups have different environment and diet, therefore the expression level of each allele of a polymorphism of a particular gene of a particular ethnic group differs, table 3.

Table 3: Allele frequency of different polymorphisms of PPARs in different ethnic groups.

Population	Gene & Polymorphism	Allele frequency in Patients (%)	Allele frequency in Control (%)	Ref.
Polish	PPARγ2, Pro12Ala	Pro/Ala, 83.5/16.5	Pro/Ala, 84.5/15.5	[32]
German	PPARα , L162V	L162V -9.4 **	L162V- 11.4 **	[35]
---	PPAR δ, +294T/C	TT-65.6, TC-30.5, CC-3.9	TT-66.7, TC-29.4, CC-4.0	[36]
Tunisian origin	PPARγ2, Pro12Ala	Pro12Ala - 12.2 **	Pro12Ala -4.1 **	[37]
Iranian	PPAR γ Pro12Ala	Ala /Ala 3, Pro/Ala 5.94 **	Ala 7, Pro/Ala, 4.06 **	[38]
Chinese	PPARγ2, Pro12Ala	Ala12Ala-0, Pro12Ala-8.9, Pro12Pro-91.1		[39]
Chinese	PPARγ2, Pro12Ala	Ala12Ala-0.2, Pro12Ala-9.4, Pro12Pro-90.4		[40]
** data not available				

4.2 The Peroxisome Proliferator-Activated Receptors Gamma (PPAR γ)

PPAR γ, a transcription factor is located on the chromosome 3, one of the T2DM locus. The gene shows a better relationship with nutrients and susceptibility to insulin sensitivity. PPAR γ locus is linked with gene-nutrient interaction, HDL, LDL and BMI.[35] A regulator of energy balance[36] is associated with early onset of extreme obesity and be a master controller of the "thrifty gene response" leading to efficient energy storage.

Pro12Ala Polymorphism

The three genotypes of Pro12Ala polymorphism of PPARγ are Pro/Ala, Pro/Pro and Ala/Ala and each influence different phenotype in different ethnic groups. Some conclude Pro12Ala a risk factor to obesity or T2DM or both, while others conclude the opposite effect for both and the association is not established due to the absence of statistically significant data (to support their conclusion).

a. Beneficial effect of Pro12Ala Polymorphisms

The metabolic effects of Ala allele or its carrier-ship subjects are influenced by FFA levels and the beneficial role of Ala allele is only due to the presence of low concentration of plasma FFA. Pro12Ala polymorphism is associated with increased insulin clearance due to reduced FFA delivery which has shown to improve hepatic insulin removal and insulin sensitivity.[37] Ala allele is associated with lipolysis which prevents release of FFAs to increase glucose uptake by muscles and Ala allele is also shown to be responsible for enhancement of insulin action to releases less FFAs.[38] If less FFAs are available, then muscle utilize more glucose due to insulin stimulation.[39]

The Ala allele may be favoring strength abilities in professional athletes and increases insulin-dependent metabolism which is a shift of the energy balance towards glucose utilization which lead to the development of a favorable weight-to-strength ratio.[40] Obese people with Ala allele have high insulin resistance due to low intake of MUFA (Establishes a correlation of insulin resistance with the clinical phenotypes of obesity and T2DM).[41] Ala allele improves insulin sensitivity and reduces diabetes risk. Ala allele polymorphism is associated with improved whole body insulin sensitivity among Swedish Caucasians. The Ala allele may predispose to the development of T2DM in obese subjects with IGT (impaired glucose tolerance test). However, changes in diet, increased physical activity and weight loss may reverse the susceptibility to some extent to improve insulin sensitivity.[42] Pro12Ala variant is not a major contributor to adiposity, fat distribution and insulin resistance in Japanese men.

A study on the effect of the Pro12Ala polymorphism on the rates of whole-body, skeletal muscle and subcutaneous adipose tissue glucose uptake in T2DM subjects found that Ala allele in obese subjects with T2DM is associated with high hepatic glucose uptake than subjects with Pro allele and the similar result is observed in non-diabetic obese subjects. Therefore, Ala allele is associated with higher hepatic glucose uptake in obese subjects.[43]

b. No association of Pro12Ala Polymorphisms

Studies suggests that there is no association between Pro12Ala polymorphism and waist circumference, weight, BMI, BP, TG but Pro12Ala polymorphism is associated with increased risk of myocardial infarction (MI).[44] There is no association between Pro12Ala polymorphism and BMI, peripheral insulin resistance and incidence and progression of diabetic complications in obese patients with long-lasting T2DM.[30] Moreover, Pro12Ala polymorphism is not associated with lipid and lipoprotein, a study from Chinese population and this may be due the appearance of very different allele frequencies: Ala/Ala absent, Pro12Ala 9% and Pro12Pro 91%.[45] A study on Dane population indicates that there is no association between Pro12 Ala and risk of Acute Coronary Syndrome (ACS) and also no association of Pro12 Ala polymorphisms with alcohol, BMI and smoking with respect to ACS.[46] Pro12Ala and T2DM development in Spanish cohort are not associated.[47] Pro12Ala polymorphism is not associated with either obesity or T2DM in Korean subjects. However, PPAR γ gene does not show any significant association with T2DM in the population of West Bengal, India may be due to small sample size.[48]

c. Disease susceptible Effect of Pro12Ala Polymorphism

Pro12Ala allele is a genetic risk factor for insulin resistance and T2DM.[49] Pro12 Ala is associated with T2DM, a HuGE review and Meta-Analysis[50] and it affects body weight and lipid homeostasis in T2DM subjects. Pro12Ala polymorphism has genetic susceptibility to T2DM and hypertension but not to insulin sensitivity in hypertensive subjects[33] and it may be an important contributor to the early onset of obesity. Moreover, Pro12Ala polymorphism is associated with obesity in non-diabetic men from Tunisian origin[51] and in obese patients, the Pro12Ala substitution is associated with elevated total plasma cholesterol and increased LDL-C. Pro12Ala polymorphisms may influence cardiovascular risk through its effects on lipid metabolism, study on obese T2DM Palestinian patients.[52] Pro12Ala is associated with increased risk of MI and independently associated with waist circumference and BMI.[53] Subjects carrying Ala allele have higher BMI and fat-mass without having metabolic syndrome by gene-gender interaction.[53] The Ala allele polymorphism is associated with reduced risk for the development of diabetes in the general population, but it may be a risk factor for insulin secretion and deficiency in individuals with T2DM. Pro12Ala is also associated with alcohol intake[54] and in the pathogenesis of obesity and T2DM.

For an age-related association studies between the Pro12Ala polymorphism and diet in obesity-related traits in children aged 10 to 12 years of Greek origin, no difference is found in obesity traits in Ala allele carriers. On the other hand, in Pro/Pro homozygous young girls, saturated fatty acid (SFA) and total fat (TF) intake is positively associated with BMI and waist circumference. Therefore, adiposity in children is influenced by Pro12Ala polymorphism in a sex-specific and age dependent manner. It is also evidence of an age-dependent gene-diet interaction in which fat intake modifies the effect of the Pro allele on obesity-related traits. On account of dietary fat intake, it seems that the Pro allele homozygotes are at higher risk for increased adiposity at a very young age which further suggests that there is an age-dependent gene-diet effect in two sexes, boys and girls.[55]

Race specific association of Pro12Ala polymorphism is found between African Americans and Whites such that Ala allele carriers have lower BMI than Whites as compared to Pro homozygote. Ala is also associated with decreased risk of incident of insulin resistance symptoms in each race.[56] A meta-analysis study suggests that, compared with non-carriers, carriers of Ala allele have significantly increased plasma total cholesterol in male subjects, marginally significant increased plasma HDL-C in healthy subjects and subjects with

genotype Ala/Ala have lower plasma TG than subjects with genotype Pro/Pro (A study on Caucasians).[57]

There is a relationship and significant association between total dietary fat with BMI which differs due to reduced activity of Ala allele.[58] Ala allele may be the independent predictors of low serum adiponectin concentrations in young Japanese men.[59] However, a significant interaction between low physical activity and Pro allele in T2DM subjects is detected in which Pro allele is significantly associated with low physical activity and high intake of PUFA. This supports the gene-environment interaction between Pro allele of PPAR γ gene and physical activity that results in increased risk of T2DM.[60] Lifestyle may modulate the effects of the Pro/Pro genotype to increase body weight and insulin resistance and thus increase the risk for T2DM.[61]

d. Protective Effect of Pro12Ala Polymorphism

Pro12Ala polymorphism has a protective role in T2DM in some ethnic group but it is a risk factor for obesity.[62] Czech individuals have protective effect of Ala allele from family history of T2DM due to high intake ratio of polyunsaturated fatty acid/saturated fatty acid, PUFA/SFA.[63] The protective effect of the Ala allele may be lost after the development of T2DM due to the increased vascular complications and β-cell dysfunction.[38] Those individuals who have a small body size at birth and are carriers of the Ala allele seemed to be protected against insulin resistance and T2DM in later life, a finding reflects early gene-environment interactions and the interaction between certain genotypes and birth size are the determinants of adult health outcomes.[64] Ala allele is also associated with insulin sensitivity and minor protective effect from T2DM - a Swedish Caucasians and Finnish study.

e. Comparison of Ala and Pro alleles

However, subjects with genotypes, Pro/Ala and Ala/Ala have significantly higher serum TG levels than those with the Pro/Pro genotype with a conclusion that the Pro12Ala polymorphism is positively associated with increased LDL in the general Japanese population.[65] Pro/Ala polymorphism is not associated with oxidized low density lipoprotein (ox-LDL) auto-antibodies in non-diabetic subjects but subjects having Ala carriers have higher levels of ox-LDL auto-antibodies than Pro/Pro genotype.[66] In obese non-diabetic patients, Ala-allele bearers have a significantly higher risk of obesity than Pro/Pro homozygotes because obese male patients carrying the Ala-allele have significantly higher BMI and plasma leptin levels compared to those containing Pro/Pro-allele. Moreover, Ala

allele carriers have lower levels of TG in Chinese population which suggests that the Pro/Ala polymorphism is associated with hypertension and TG levels[67] but subjects with Pro/Ala genotype have significantly higher body weight than those with Pro/Pro genotype.[68]

PPAR γ C161T polymorphism also has moderate protective effect on CAD among Chinese ethnic group but not among Caucasians[69] and C161T C/T genotype shows different effect on serum lipid profile in CHD patients having diabetes and this effect is very less in the presence of Pro12Pro genotype.[70]

4.3 The Peroxisome Proliferator-Activated Receptors Alpha (PPARα)

PPARα is mainly present in liver where it regulate nutrient metabolism, such as fatty acid oxidation, gluconeogenesis, and amino acid metabolism. The allelic variants of PPAR*α* can influence the risk of CAD (Coronary Artery Disease) due its effect on lipid metabolism. PPARα has an increasing effect on total cholesterol and LDL-C levels in non-diabetic CHD (Coronary Heart Diseases) patients. However, PPARα polymorphism may have diverse effects on serum lipids and CHD risk. Polymorphism of PPAR α influences subjects of IGT to T2DM[71] and its polymorphisms have an association with physical activity also.

L162V Polymorphism of PPARα

There is an increasing potential connection between polymorphisms of PPARα and obesity.[72] The polymorphism of PPARα, L162V has been associated with LDL, HDL levels, increased TG and abdominal obesity.[73] Selective PPAR α agonist increases HDL level and decreases TG level. V162 allele is associated with reduced levels of HDL-C in cardiovascular risk subjects of insulin resistance and T2DM.[74] Carriers of the V162 allele are more prevalent among alcohol consumers and there exists a significant association between the L162V polymorphism and alcohol consumption.[75] C allele of L162V, a rare allele is associated with higher HDL, lower TG and VLDL levels compared to G allele.[76] Race modifies the associations of L162V with TG Levels in African-American but not Caucasian. L162V is less prevalent in African-Americans than in Caucasians and L162V in African-Americans is associated with higher plasma lipoproteins and TG levels.[77] L162V polymorphism is associated with atherosclerosis through IL-6.[34] V162V is associated with increased fasting serum total cholesterol concentrations, a study on middle-aged whites which gives no significant association between the L162V polymorphism and obesity and T2DM. V162V polymorphism may, however, confer an increase in fasting levels of serum lipids[78]

and L162V polymorphism seems to be associated with atherosclerosis.[34] V allele of L162V polymorphism of PPARα is associated with TG in White males.[79]

V227A polymorphism of PPARα in Japanese population is associated with alcohol drinking.[80] There is a strong evidence that polymorphism of PPARα gene may influence the risk of MI in a European population.[81] Analysis of L162V polymorphism of PPARα gene is associated with susceptibility to high VLDL and low HDL because of Leu/Val genotypes.[82] The V227A polymorphism of PPARα locus is also associated with serum lipid concentrations and modulates the association between dietary PUFA intake and serum HDL concentrations in Chinese women population.[83]

The association of allelic variants G/C at intron 7 of the PPARα gene with CAD examined in a hospital-based Indian population shows a positive association with CAD and dyslipidemia.[84] L162V and intron7G>C polymorphisms are in linkage disequilibrium and C allele of Intron7G>C polymorphism is associated with higher HDL, lower TG and VLDL levels compared to G allele. This is a protective role of intron7G>C polymorphism in the development of CVD in Brazilian population.[76]

4.4 The Peroxisome Proliferator-Activated Receptors Delta (PPAR δ)

PPAR δ is mapped to 6p21.1-6p21.2, expressed ubiquitously with nine identified polymorphisms, four in the introns, one in 5' un-translated region and four in the 3' un-translated region. PPAR δ is involved with keratinocyte differentiation, wound healing, mediates VLDL signaling[85] and fat metabolism.[86] Studies provide evidence for a protective effect of PPAR δ in terms of HDL cholesterol and BMI in male population. PPAR δ influences cholesterol metabolism in men and also implicated with cardiovascular problems.[87] Activation of PPAR δ plays an important role in protecting pancreatic β-cells against lipotoxicity in metabolic syndrome and T2DM.[88] PPAR δ polymorphism is clearly associated with a phenotype of reduced stature in both adults and children. PPAR δ may affect height through altered metabolic efficiency.[89] There is a differential effects of PPAR δ in males and females[90] and PPAR δ may not be linked with obesity and T2DM directly but it is having several positive associations with fasting plasma glucose and BMI.[91]

T+294C polymorphism of PPAR δ

The effect of this polymorphism on ethnic group may be modulated by environmental factors, obesity, ethnicity, ratio of unsaturated to saturated fatty acids and genetic background. The

T+294C polymorphism of PPAR δ is associated with low HDL-C. HDL plasma levels are inversely related to BMI and its C allele carriers have higher LDL level in plasma.[92] The C allele of this polymorphism is significantly associated with a lower abdominal obesity.[93] There is no significant interaction between +294T > C genotypes and alcohol consumption.[94] The C allele of T-842C polymorphism of PPAR δ is significantly associated with increased risk to kidney diseases.[95]

4.5 Gene-Gene interaction

Studies provide evidence of the interaction between polymorphisms and the metabolic responses to the diets.[96] Polymorphism of PPAR δ, +294T/C is associated with BMI and interacts with polymorphism of PPARα L162V to show obesity is polygenic.[97] Pro12Ala polymorphism may result in protection against liver injury but L162V polymorphism may be involved in the progression of NAFLD.[98] PPAR-α L162V and PGC-1A G482S polymorphisms are associated with alcohol consumption in Mediterranean population.[75] G482S polymorphism shows a significantly higher frequency in high alcohol drinkers than in non-high alcohol drinkers. However, an effort to find association between +294TC and L162V polymorphisms failed with no gene–gene interaction between the PPAR δ +294TC and the PPARα L162V polymorphisms.[99] A recent finding strongly suggests that the genetic variation in PPARG and ADIPOQ loci could contribute to the risk for the development of T2DM in Indian Sikhs population.[100]

San Luis Valley Diabetes Study on female patients shows that C161T appears to be a better predictor of fasting insulin levels and insulin resistance than Pro12Ala.[101] PPAR γ exon 2 and exon 6 gene polymorphism are not associated with the development of diabetic nephropathy in Turkish T2DM patients.[102] Pro12Ala polymorphism affects body weight and the effect is prevalence with the presence of T allele of C161T polymorphism.[68] In French Caucasians, the combined effect of PPAR γ Pro12Ala and adiponectin gene, *APM1* G-11391A polymorphisms show no interaction of genes on the risk of subjects of six-year hyperglycemia.[103] PPAR δ and PPAR γ haplotypes are independent determinants of plasma levels of lipids, severity of coronary atherosclerosis.[104] Pro12Ala and Pro115Gln mutations in the PPARγ2 gene are not significantly associated with obesity and T2DM. Polymorphisms of Adiponectin gene, SNP11377 and SNP276 are also associated with the increased risk of T2DM[105] and PPAR α and PPAR γ Polymorphisms are also the risk factors for dyslipidemia in Chinese Han population.[106]

5. SUMMARY AND CONCLUSION

It is evident from the review that PPARs are strongly associated with lipid profile, BMI, obesity and T2DM in many ethnic groups except very few due to the gene-environment and gene-diet interaction. Ala allele is strongly associated in the susceptibility to obesity with minor different effect with T2DM subjects, slightly protective. However, the protective effect of Ala is lost due to diabetic complications and poor allele frequency in all ethnic groups (mutant allele). All the polymorphisms of PPARs are strongly associated with intake of alcohol except +294T/C polymorphism of PPAR δ (not associated with alcohol intake). In conclusion, PPARs (alpha, gamma and delta) are strongly associated in the susceptibility to obesity and T2DM with a minor protective effect of Ala allele on T2DM subjects. PPAR gamma also shows beneficial effect due to gene-diet interaction.

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