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Inter-ethnic variations in association of TNF-alpha g308a single nucleotide polymorphism with type 2 diabetes mellitus-a review

Summary

According to World Health Organization, the prevalence of diabetes mellitus (DM) is on the rise. Tissue necrosis factor- alpha (TNF-α) is one of the inflammatory markers which play role in the pathogenesis of DM. Single nucleotide polymorphism (SNP) at 308G/A has been reported to be associated with type 2 DM. Frequency of TNF-α G308A polymorphism was determined in different ethnic groups and is found to be highly variable. Limited number of studies reported a positive association between type 2 DM and TNF-α SNP and many studies; including meta-analyses failed to find such association. TNF-α G308A polymorphism has been found to be associated with insulin resistance and BMI, although these findings are challenged by many studies. The probable explanation of higher BMI is the association of presence of TNF-α G308A polymorphism with higher rates of lipid synthesis, and suppression of FFA levels in obese persons. There is no single explanation for such highly variable results in different ethnic groups. Presence of yet unidentified gene polymorphism in linkage disequilibrium with TNF-α gene polymorphism could be responsible. The different results can also be contributed to the fact that the study groups differ in age, gender distribution, age of onset of disease, life style, degree of obesity and glucose tolerance. Comprehensive genetic studies of whole TNF-alpha promoter area are required to be done in large population samples in different ethnic groups. Polymorphisms are usually co-related in a complex manner and are co-inherited and conclusions are difficult to be drawn on small sample size.

Keywords: tissue necrosis factor alpha, diabetes mellitus; world health organization, polymorphisms, diabetes mellitus, metabolism, insulin, TNF-α, patients, type 2 dm

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Introduction

According to World Health Organization (WHO) and International Diabetes Foundation, the prevalence of diabetes mellitus (DM) is on the rise. It was 100-135million individuals worldwide in 1994-1995, increased to 171million in 2000 approximately 246million in 2007 and 289million (6.4%) in 2010.[1] The prevalence is expected to increase up to 439million (7.7%) by the year 2030.[2] Diabetes mellitus is a metabolic disorder of multiple etiologies characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects from insulin secretion, insulin action, or both. Inflammatory markers play role in pathogenesis of type 2 DM. G308A promoter single nucleotide polymorphism (SNP) of TNF-α gene was found to be associated with type 2 diabetes mellitus. TNF-α G308A polymorphisms also associated with serum TNF-α levels, insulin resistance, insulin levels, body mass index, and lipid profile. There is inter- ethnic variations; not only in the frequency of this polymorphism in type 2 diabetics and healthy populations but also in association with type 2 DM, serum TNF-α levels, insulin resistance, body mass index, and lipid profile, reported in international studies. The present review analyzes these inter-ethnic variations and determines possible causes of these variations. A total of 45 full text articles on the subject conducted from 1995-2012, found on electronic sources were reviewed.

Role of inflammation in pathogenesis of dm

The rapid increase in type 2 DM incidence in last decade indicates significant role of environmental and dietary factors in addition to genetic factors. Obesity is strongly associated with type 2 DM. Obesity is considered as chronic low grade inflammatory state and markers of sub clinical inflammation increase in the blood of type 2 DM patients many years before diagnosis of the disease.[3] These markers play a considerable role in pathogenesis of type 2 DM, obesity, insulin resistance and apoptosis of beta cells of endocrine pancreas and include interleukin-6 (IL-6), IL-1, IL-18, TNF-α, C-reactive protein (CRP), tissue plasminogen activator (TPA), heptoglobulin and fibrinogen.[3]

TNF-alpha

TNF-α has multiple mechanisms. It stimulates IL-6 release and directly inhibits insulin signaling by phosphorylation at serine 307 residue of IRS-1. It also induces transcription factor nuclear factor (NF)-kappa B which causes apoptosis of beta cell of pancreas. TNF-α also increases elevated serum free fatty acids (FFA) levels.[4] Local inflammation in obese adipose tissue was first reported in 2003.[1] Elevated serum levels of TNF-α are found in type 2 DM patients and in obese healthy persons who subsequently developed type 2 DM in a span of 2-4 years indicating the future risk of metabolic syndrome and type 2 DM.[3,5–7] Adipocytes contribute almost all of TNF-α and explain the association of high TNF-α level with obesity and raised body mass index.[7,8] Indirect studies also indicate exercise and weight loss can lead to decreased concentration of TNF-α.[7,9] High levels of TNF-α have been reported to be associated with insulin resistance.[9–11]

TNF α renders insulin resistance by interfering with insulin signaling in adipocytes and hepatocytes. TNF-α causes insulin resistance in skeletal muscle too by impairing glucose uptake and translocation of glucose uptake transporters (GLUT-4).[12] Hyperinsulinemia itself induces augmented production of TNF-α in serum in obese type 2 DM patients.[9–13] High glucose uptake results in apoptosis of beta cells in pancreas with increase expression of IL-1 B messenger ribonucleic acid (mRNA) and its levels. IL-1B pro apoptotic effects are found to be mediated by augmenting IL-6.[14] TNF- α also has pro-apoptotic effect by activation of transcription factor nuclear factor (NF)-kappa B target genes in cultured beta cells of pancreas.[15]

TNF-alpha single nucleotide polymorphism

TNF-α gene is located on 21.3 locus on short arm of chromosome number 6 (6p 21.3), span about 3kb and contains 4exons. The gene lies in the class III region of major histo compatibility complex (MHC), 250kilobases centromeric of the HLA-B locus and 850 kilobasestelomeric of HLA-DR. The gene codes for TNF-α as 157 amino acid polypeptide processed from 233 amino acid precursor. The -308 A allele of TNF- α lies on the extended haplotype HLA-A1-B8-DR3-DQ2.[16] The frequency of TNF-α-308A allele was found to be variable in different ethnic groups (Table 1) (Table 2).

Table 1 Frequency of TNF-Alpha G308A Polymorphism in Different Ethnic Groups

S. No.	Ethnic group	N	TNF-alpha genotype			Reference
			GG(%)	GA(%)	AA(%)	
1	Obese Asian Indian	201	90.5	9.5	nil	Bhagat et al.[35]
	Non-obese Asian Indians	143	95.1	4.90%	nil	
2	Diabetic South Indians	330	10.6	86.4	3	Kolla et al.[34]
	Healthy South Indians	250	2	94	4	
3	Spanish	313	86		14	Carbalan et al.[57]
4	Obese Polish	121	52.89	46.28	0.8	Wybranska et a.[43]
5	Finnish	490	74	25	1	Kubaszek et al.[17]
6	Australian	170	31	64	5	Morris at al.[31]
7	Healthy Taiwanese	246	84.2	15.4	0.4	Sheu et al.[41]
8	Obese Australian	180	76	24		Dalziel et al.[45]
9	Germens	176	67	30	2.84	Brand et al.[55]
10	Obese Romans	115	86.9		13.1	Romeo et al.[51]
	Lean Romans	79	85.4		14.6	
11	Healthy Hong Kong Chinese	121	92.6	7.4		Lee et al.[50]
	Diabetic Hong Kong Chinese	440	91	9		
12	Young healthy Japanese	122	96.7		3.3	Ishii et al.[58]
	Old healthy Japanese	177	97.2		2.8	
	Diabetic Japanese	177	97.2		2.8	
13	Healthy French	710	85		15	Hermann et al.[54]
14	Belfast		76		24	
15	Healthy Belgarians	62	66	25.8	8	Louis et al.[38]

Table 2 Inter-Ethnic Variations in Frequency of TNF-Alpha -308A Allele

Ethnic group	TNF- alpha -308 A allele(%)	Reference
Diabetic Japanese	2.2	Yamashina et al.[18]
Caucasian Whites	45	Sookoin et al.[16]
Healthy Finnish	36	
Healthy Brazilians	23	
Healthy Chinese	18	
Healthy Japanese	3	

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Table continued...

Ethnic group	TNF- alpha -308 A allele(%)	Reference
Healthy Irelanders	24.2	
Healthy Swedish	15.8	
Diabetic Chinese	8.7	Wang et al.[39]
Non-diabetic Chinese	7.4	
Non-diabetic Japanese	1.5	
Diabetic Japanese	1.4	
Diabetic Swedish	35	Li et al.[23]
Healthy Swedish	33	
Danish & Spanish	18.9	Rasmussen et al.[30]
White & African Americans, British	19	Fernandez-Real et al.[42]
Australian, French & Irish	19	Wilson et al.[36]

TNF-alpha G308A polymorphism and type 2 dm

Association of TNF-α G308A allele with pathogenesis of type 2 DM is explained by the fact that -308A allele is responsible for increased transcription of TNF-α as compared to -308G allele as high as two folds leading to increased serum levels of TNF-α.[17] High levels of TNF-α play its role in the pathogenesis of type 2 DM by the mechanisms mentioned above. Genetic studies on association of TNF-α G308A polymorphism with type 2 DM, serum TNF-α levels, insulin resistance and obesity however, reveal conflicting results. Association between TNF-α G308A with type 2 DM has been found to be positive in Japanese and in older diabetic subjects from Netherlands.[18] In these individuals, risk of type 2 DM was 4.6 folds higher in homozygous 308AA allele and 0.9 folds higher in 308GA allele. The risk estimate for AA genotype was 6.5 among men and 3.0 among women.[19] Risk of type 2 DM was found to be increased by two folds by -308A allele in Finnish population. In fact, 12.6 % of overweight IGT subjects with 308GG and 20.7% of subjects with 308A allele developed type 2 DM.[20]

No significant association was found in type 2 DM and TNF-α G308A polymorphism in diabetic Americans,[21] Greeks,[22] Swedes,[23] Chinese,[24,25] Koreans,[26] British,[27] Taiwanese,[28] Japanese,[29] Danish Caucasians[30] and in obese Australians.[31] In a recent study on Tunisian population, TNF-α SNP was not found to be associated with type 2 DM.[32] In a meta-analysis of 18 studies; comprising of 7611 type 2 DM and 6944 healthy controls, no association was found between TNF-α G308A polymorphism and DM.[33] The frequency of TNF-α genotypes in South Indian diabetic patients was found to be GG 10.6%, GA 86.4% and AA in 3% while in healthy controls, it was GG 2%, GA 94.5% and AA 4%,[34] indicating no significant association of DM and polymorphism. In another study, on obese and non-obese healthy Indian Asians, GA genotype was found to be 9.5% and 4.9% respectively.[35]

TNF-alpha G308A polymorphism and serum TNF-alpha levels

Production of TNF-α is regulated at transcription, post-transcription and translation levels. In response to various stimuli like lipopolysaccharides (LPS) stimulation of macrophages, TNF transcription increases 3folds TNF mRNA increases to as high as 100 folds. This leads to synthesis of TNF-α increased by a factor of ~10,000 at translation level.[36] Slight change at transcription level can markedly change the serum levels of TNF-α. The role of TNF-α G308A polymorphism as a much stronger transcriptional activator and its association with increased serum TNF-α levels was first described in 1997 in human B cell line. Wilson et al.[36] demonstrated that there was no difference in the affinity of DNA-binding proteins between G and A allele, indicating direct effect of polymorphism on gene regulation where as in another study, it was demonstrated in cell cultures that TNF-α 308A allele leads to greater affinity of nuclear factor to promoter area resulting in two fold increase in transcription and ultimately higher serum levels.[37] Similarly, LPS stimulated release of TNF-α in whole blood cell culture was found to be augmented in the presence of 308A allele.[38] TNF-α 308A allele was found to be associated with higher reporter gene activity and also increased TNF-α production in whole blood cell cultures.[19] TNF-α 308A allele was found to augment the TNF-α transcription, increased TNF mRNA in adipose tissues and increased serum TNF-α levels; leading to increased susceptibility to type 2 DM. Serum TNF-α levels in TNF-α -308A allele carriers were found to be increased 2 folds in overweight Finnish subjects,[20] in Danish Caucasians,[30] in Chinese[39] and in American females[9] The difference in S. TNF-α levels based on genotype was observed neither in healthy controls, impaired glucose tolerant and diabetic Czech Caucasians[40] nor in healthy Chinese.[41]

TNF-alpha G308A polymorphism and insulin resistance

Association between G308A polymorphism and insulin resistance again show variable results although higher levels of TNF-α in -308A allele carrying subjects is expected to cause increased insulin resistance. The association was found to be positive in obese middle-aged male and female Spanish subjects; more marked in females and serum insulin levels were higher in both -308 GA and AA allele carriers,[42] in obese female Polish Caucasians[43] and in diabetic obese Canadian patients, but not in non-obese diabetic Canadians.[44] Positive association between 308 A allele and insulin resistance was also found in obese Australians.[45] There was also strong negative association between 308 A allele and S. HDL-cholesterol, although

insulin resistance was positively associated with BMI and waist circumference (WC) in all obese irrespective of G or A allele in obese Australians.[45] No significant differences by polymorphism carrier status were found for insulin resistance in Australian females,[46] in diabetic Japanese patients,[29,47] in Danish Caucasians,[30] in obese Americans,[48] in young healthy relatives of type 2 diabetic German Caucasians,[49] in Hong Kong Chinese,[50] in obese and lean Romans[51] and in overweight IGT Finnish subjects.[20] This association was neither found in relatives of type 2 diabetic British Caucasians and in controls[52] nor in type 2 diabetic subjects from New England.[21] In healthy Chinese, no difference in insulin resistance based on allele frequency was found.[41]

TNF-alpha G308A polymorphism and bmi

TNF-α 308 G/A polymorphism has been found to be associated with higher BMI, although this finding is challenged by many studies. The probable explanation of higher BMI is the association of presence of TNF- α G308A polymorphism with higher rates of lipid synthesis, and suppression of FFA levels in obese persons but not in non-obese healthy persons. Interestingly, TNF-α a allele was associated with augmented glucose oxidation in non-obese healthy subjects but not in obese subjects.[53] This indicates the differential effect of TNF-α -308 A allele on lipid and glucose metabolism in obese and non-obese subjects.

Association between TNF-α G308A polymorphism with obesity has been found in obese diabetic and non-diabetic French and Irish subjects than those controls with 308G allele.[54] This positive association was also found in obese Spanish population,[42] in male Polish Caucasians,[43] in Germens[55] and in obese Swedish females with AA genotype.[56] 308A allele showed a 23 percent increased risk of obesity in a meta- analysis of 3562 individuals from 08 studies. 16 TNF-α allele was found to be associated with higher BMI, waist and hip circumference and total body fat in obese Spanish Caucasians.[57] However, 308A allele was not associated with obesity in Australian females,[46] in diabetic and non-diabetic subjects from New England,[21] in obese Caucasians and African Americans,[48] in diabetic Japanese,[58] in obese Chinese,[39] in elderly Chilean women,[59] in healthy Tunisians,[60] in obese and lean Romans[51] and in obese Australians.[31] TNF-α -308A allele did not affect the amount of weight loss in male and female Danish Caucasians in another study.[30]

The association between TNF-α-308 heterozygous GA with higher S. FFA levels as compared to GG genotype has been found in Chinese non-diabetics,[33] although in another study, A allele was associated with higher lipid synthesis and suppressed FFA levels in over-weight Finnish subjects though, the same allele was associated with higher glucose oxidation but not with higher lipid synthesis or suppressed FFA levels in non-obese healthy Finnish subjects.[53] Percent body fat was found to be increased in the presence of A allele in obese Spanish population[42] whereas Obese Chinese with GG genotype had lower HDL cholesterol than carriers of GA or AA genotype.[39] TNF-α a allele was not associated with BMI or lipid profile in Hong Kong Chinese with metabolic syndrome in another study.[50] In older, but not in young diabetic Japanese men, TNF polymorphism was found to be associated with higher TG and lower HDL levels.[58] In overweight IGT Finnish subjects, simultaneous polymorphism in IL6 G174C and TNF-α G308A showed a 2.2 fold increase risk of type 2 DM than neither of SNP, although risk was not higher in simultaneous SNP's as compared to 308A SNP alone.[20]

Possible reasons for varying results in association of TNF-alpha G308A SNP with type 2 DM inter-ethnically

The underlying reasons for conflicting results in different ethnic groups regarding association between TNF-alpha G308A polymorphism with type 2 diabetes mellitus, serum TNF-α levels, insulin resistance and BMI in diabetic, IGT and healthy subjects are not fully known. Association of TNF-α-308 G/A polymorphism with diabetes mellitus and insulin resistance show inconsistent results. One explanation for association of this SNP with DM is increased insulin resistance caused by raised serum levels of TNF-α. The fact that TNF-α a allele leads to augmented transcription and higher serum levels is very strongly supported by in vitro studies on cell culture, cell lines and on animal models. Production of TNF-α is regulated at transcription, post-transcription and translation levels. In response to various stimuli like lipopolysaccharides stimulation of macrophages, TNF transcription increases 3-folds, TNF mRNA increases to as high as 100 folds. This leads to synthesis of TNF-α increased by a factor of ~10,000 at translation level.[36] Slight change at transcription level can markedly change the serum levels of TNF-α. The presence of a allele at 308 position is one of those factors which augments the transcription and ultimately translation, thus resulting in higher serum levels of TNF-α.

Despite quite large number of studies on association of DM with this SNP, insulin resistance and BMI; very few studies correlated the serum levels of TNF with insulin resistance, BMI or risk of DM. Association of A allele with higher serum levels of TNF has been reported in overweight Finnish subjects,[20] in Danish Caucasians,[30] in Chinese[39] and in American females.[9] Negative association has been reported in healthy controls, impaired glucose tolerant and diabetic Czech Caucasians[40] and in healthy Chinese.[41] It is well documented that insulin resistance is associated with BMI but when catering for genotypes, A allele association with insulin resistance in presence of obesity but not in absence of it, has been reported in diabetic Canadians.[44] Interestingly not many studies were found in literature indicating positive association of a allele presence with higher insulin resistance even in absence of obesity. In one study, insulin resistance was found greater in both obese and lean Romans[51] in either allele carriers. It may indicate the possibility that insulin resistance may be secondary to raised BMI, in all obese irrespective of genotype; the fact supported by studies on obese Australian,[44] obese Americans,[48] overweight IGT Finnish subjects[20] and obese female Polish Caucasians,[43] in which insulin resistance was present in obese subjects carrying either allele. TNF-α polymorphism may act as a genetic factor enhancing the insulin resistance in presence of obesity, irrespective of serum TNF-α level as found in many studies. Why in some studies, this association between polymorphism and insulin resistance is not found even in presence of obesity is not known.

Variable results regarding TNF-α SNP at -308 in different ethnic groups might be due to yet another unidentified functional gene polymorphism in close linkage disequilibrium with TNF-α G308A polymorphism. In support of this hypothesis, an association between B-9 allele of AG/GT dinucleotide repeat polymorphism of TNF-α gene and diabetic retinopathy in Southern Indian population has been reported.[61] Similarly, polymorphism of a stress protein gene; P2/P2 genotypes of heat shock protein 70-2 is found to be close to and in linkage disequilibrium with TNF-α promoter area and is statistically associated with obesity in Tunisian subjects.[60]

Contribution of other, yet unidentified DM susceptibility genes in insulin resistance and beta cell failure is also being explored. Pro-inflammatory and anti-inflammatory cytokines interact with each other and play role in altering beta cell functions and TNF-α gene may influence this interaction. Moreover, there could be additional, still unidentified risk factors which obscure the impact of SNP with specific genetic background in various ethnic groups. The life style and average age of onset of DM in different ethnic groups may affect the impact of polymorphism in susceptibility of the disease. The different results can also be contributed to the fact that the study groups differ in age, gender distribution, life style, degree of obesity and glucose tolerance. Single nucleotide polymorphism may be considered as a susceptibility factor in certain population segments based on other risk factors and comprehensive studies with large number of sample size may indeed be required to statistically manifest SNP-related risk factors. Most of the studies are done in relatively small population groups which might include patient selection biases and do not reflect the general risk of population. Comprehensive genetic studies of whole TNF-alpha promoter area are required to be done in large population samples in different ethnic groups. Polymorphisms are usually co-related in a complex manner and are co-inherited and conclusions are difficult to be drawn on small sample size.

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Conflict of interest

Author declares that there is no conflict of interest.

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