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Tumor necrosis factor-alpha 308 G/A polymorphism and type 2 diabetes mellitus; a systematic review and meta-analysis

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ABSTRACT

Context: Type 2 diabetes mellitus (T2DM) is a multi-factorial disease with several genetic and environmental factors known to be associated with the disease. Tumor necrosis factor-alpha (TNF-α) acts on fat cells associated with increased insulin resistance and obesity and its increase can be associated with the prevalence of T2DM. Previous studies on the relationship between 308 G/A polymorphism in TNF-α and T2DM were not conclusive. The aim of this study was to investigate the association between 308 G/A polymorphism in TNF-α gene and T2DM using a systematic review and meta-analysis.

Evidence Acquisitions: In this systematic review we searched all published studies about the association between TNF 308 G/A polymorphism and T2DM through databases such as Scopus, Science direct, PubMed and Google scholar. A fixed or random effect model was used on the basis of heterogeneity. The heterogeneity was assessed using the I^2 index. We used STATA software (version 11.2) for data analysis.

Results: In 22 selected papers, the total number of T2DM and control subject was 8485 and 8615, respectively. Odds ratios (ORs) with 95% confidence intervals(CI) for the GG genotype polymorphism 308 G/A in total, Asian populations and whites (Caucasian) were estimated as OR = 0.98 (95% CI: 0.96-1.00), OR = 0.96 (95% CI: 0.93 to 0.99) and OR =1.00 (95% CI: 0.97 to 1.40). The Publication Bias/or heterogeneity was observed in this study.

Conclusions: The present investigation have shown that 308 G/A polymorphism GG and GA genotypes in TNF-α gene cannot be considered as predictors of T2DM ($P < 0.05$).

Implication for health policy/practice/research/medical education:
In a systematic review on 22 selected papers, we found that 308 G/A polymorphism GG and GA genotypes in TNF-α gene cannot be considered as predictors of type 2 diabetes mellitus ($P < 0.05$).

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Review

1. Context

Diabetes mellitus (DM) is a chronic disease and is one of the health challenges in the 21st century. Decrease in insulin secretion and/or resistance to it are known to be involved in the development of DM (1). In general, DM refers to a heterogeneous group of metabolic disorders characterized by decreased insulin action or resistance to it, or both and is divided into two main categories; diabetes type 1, and type 2. DM is generally characteristic by insulin resistance and decrease in insulin production (2). Approximately 90% of the global epidemics of DM belongs to type 2 DM (T2DM) and it has become the fourth common cause of death in most developed countries. According to the international diabetes

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federation in 2003, the proportion of diabetes, in the world, was 194 million people and it is estimated this number will increase to 366 million people in 2030 which will be mostly T2DM. Thus, due to increased demand for health care and the imposition of economic pressures, diabetes (more specifically T2DM) has become an important challenge for different communities (3).

There are known factors predisposing individuals to T2DM. It is a multi-factorial disease and several factors both genetics and environmental play role in its development. Because of the magnitude, complexity and multi-factorial nature of diabetes, the accurate diagnosis of the genetic factors is difficult. Gene polymorphisms have been considered to be essential for the development of disease. Genomic studies in several countries and different races have been performed to identify genes associated with T2DM (4-6). However, the exact gene (/or genes) involved in T2DM is not recognized. It seems that all genes involved in the pathway of insulin biosynthesis in pancreatic insulin and obesity can be the potential candidates (7). So far, more than 200 genes have been identified. One of these genes is tumor necrosis factor-alpha (TNF-α). As a regulator, TNF-α acts in fat cells and is associated with increased insulin resistance and obesity (8). Adipose tissue is an important source of TNF-α. Thus TNF-α expression in human adipose tissue and muscle increases the risk of obesity (9,10).

One of the known polymorphisms in tumor necrosis factor-alpha (TNF-α) gene that is located on the short arm of chromosome 6, is the displacement of guanine with adenine at position 308 promotes the mentioned gene. In general, the results of studies on the association between the TNF-α gene polymorphism and T2DM is inconsistent because in different populations different results have been found (11)

Today's chronic diseases are major challenges for governments, nurses, healthcare professionals, families and the community (12-17). So, many social and economic costs are imposed annually on the family and society (18,19).

Despite many studies conducted in this field, in different countries and races, the existence or lack of relationship between 308 G/A polymorphism of TNF-α and the risk of T2DM has not been clearly demonstrated. The aim of this study was to investigate the association of 308 G/A polymorphism in TNF-α gene and T2DM using a large-scale meta-analysis.

2. Evidence Acquisitions

2.1. Literature search and study selection

To find related documents, we searched the following literature databases: Scopus, PubMed, and Google scholar, SID, Irandoc and Magiran. We performed article search mainly using systematic search for all possible combinations of English key words, the major and sensitive ones and their equivalent keywords. We searched based on keywords; TNF-α, type 2 DM and polymorphism. To determine the scope of this study, case-control studies and meta-analysis of previous articles were collected. The article selection was as follows; 1) a related case-control study and 2) having complete data about genotype and adequate alleles. All searches were performed independently by two people. Under this process, in initial inquiry we found 37 articles conducted during 1995 to 2013. The main criterion to select papers in this study, was referring to the association between gene, polymorphisms of TNF-α with T2DM. We added all relevant papers to the initial list. Studies about clinical decision making or those about clinical characteristics of patients or those not related to the topic of the research are excluded. The 8 non-relevant articles were removed and 29 articles' abstracts were investigated. Due to the unavailability of full texts, the 2 papers' abstracts were deleted and the full texts of 27 articles were investigated for the quality and finally, 22 articles were analyzed (Figure 1).

2.2. Statistical analysis

We extracted from each article the following data; the number of controls, number of cases, the presence of genotypes GG, GA and AA polymorphism 308 G/A in cases and controls, age, sex and year of publication

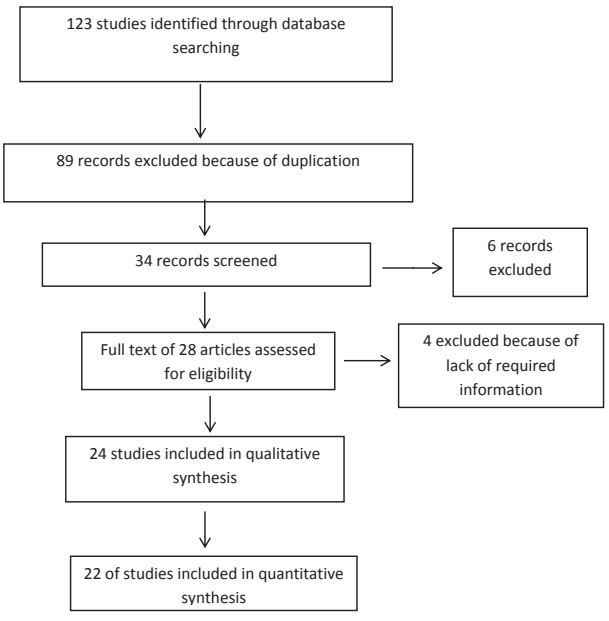

Figure 1. Study flowchart.

of the paper. Odds ratios (ORs) and its 95% confidence intervals (CIs) were calculated for each study.

Peto method was used to calculate OR and pooled OR. The heterogeneity was assessed using the Q and I^2 indexes. Begg's funnel plot was used to check publication bias. The data were analyzed using R program (version 2/15/1) and Stata (version 11.2). Additionally *P* value less than 0.05 was considered as statistical significance.

3. Results

In 22 reviewed papers, the total number of T2DM and control subjects were 8485 and 8615, including 6003 cases and 5683 controls with genotype GG, 2136 cases and 2433 controls with GA. AA genotypes were found among 198 cases and 408 controls. The European, Australian, Mexican, Japanese, Indian, Chinese, Brazilian, Chilean, and Iranian populations have been studied from 1995 to 2013. Characteristics of the studies are summarized in Table 1.

According to the results from the Random Effects Model, OR (0.99) and 95% CIs (from 0.97 to 1.01) were estimated. There was no significant association between GG genotype and T2DM ($P > 0.05$). Due to the heterogeneity of the studies (I^2 Index=1.82), the CIs for each study based on a Random Effects Model is given in Figure 1.

The results of three studies carried out by Zeggini et al,[27] Guzmán-Flores et al,[22] and Golshani et al, to GG genotype illustrate its protective role against T2DM (Figure 1), while in study conducted by Boraska et al,[26] it has been indicated that individuals having GG genotype are 1.46-folds higher at risk of T2DM. In the 17 studies, there was no significant difference between GG genotype and the susceptibility to T2DM. Combining the results of all 21 studies, it has been shown no significant relationship between GG genotype polymorphism 308 G/A genes in TNF-α and susceptibility to T2DM (Figure 1).

In Figure 2, we found the publication bias has no influence on GG genotype indicated by the symmetry of the funnel. The size of the circles has shown the precision of the studies. Thus, the greater the circles, the greater the samples sizes, and vice versa (Figure 3).

4. Discussion

The results of the present study have shown that 308 G/A polymorphism GG and GA genotypes in TNF-α gene cannot be considered as predictors of T2DM

Table 1. The characteristics of different articles related to 308G/A (TNF-α) and susceptibility to type 2 diabetes mellitus

Authors' name	Publication year	Country	Case (n)	Control (n)	Case/Control (age year)	GG		GA+ AA		References
						Case	Total	Case	Total	
Heijmans et al	2002	Netherlands	79	577	>85	51	429	28	227	(20)
Perez-Luque et al	2012	Mexico	95	135	49.5/52	72	188	23	42	(21)
Guzmán-Flores et al	2011	Mexico	518	1290	—	438	1581	80	227	(22)
Li et al	2003	Finland	395	284	65.7/55.0	273	462	122	217	(23)
Furuta et al	2002	Japan	132	142	55.6/51.8	129	268	3	6	(24)
Bouhaha et al	2010	Tunis	228	300	43.8/60.6	204	345	95	149	(25)
Boraska et al	2010	UK	1454	2504	—	938	2571	516	1387	(26)
Zeggini et al	2005	UK	834	1231	—	484	1263	292	726	(27)
Kim et al	2006	Korea	169	198	—	174	315	24	52	(28)
Lindholm et al	2008	Sweden	2957	206	61.2/59.7	1908	2041	1019	1091	(29)
Ishii et al	2000	Japan	71	299	58.76/41.96	69	359	2	11	(30)
Morris et al	2003	Australia	91	189	—	52	178	38	101	(31)
Liu et al	2008	China	245	122	48.2/46.5	222	331	23	36	(32)
Hamann et al	1995	German	138	57	57.9/56.1	108	154	30	41	(33)
Padovani et al	2000	Brazil	21	145	43/42	17	128	4	38	(34)
Ko et al	2003	China	339	202	38.2/36.8	284	455	55	86	(35)
Santos et al	2006	Chile	30	53	69–60	27	72	3	11	(26)
Shiau et al	2003	China	261	189	58.73/58.16	218	386	39	58	(37)
Tsiavou et al	2004	Greece	32	39	51/44	29	61	3	10	(38)
Vendrell et al	2003	Spain	135	207	56.67	109	268	26	74	(39)
Dutta et al	2013	India	122	100	—	76	147	46	75	(40)
Golshani et al	2013	Iran	173	173	50.4/54.1	146	308	27	38	Unpublished
Total			8485	8615		6003	12310	2498	4703	

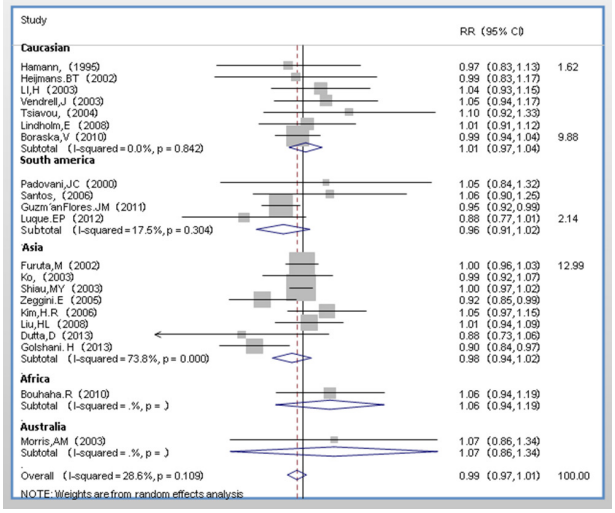

Figure 2. Meta-analysis of the GG genotype308G/A with T2DM. Square represent effect estimate of individual studies with their 95% confidence intervals with size of squares proportional to the weight assigned to the study in the meta-analysis

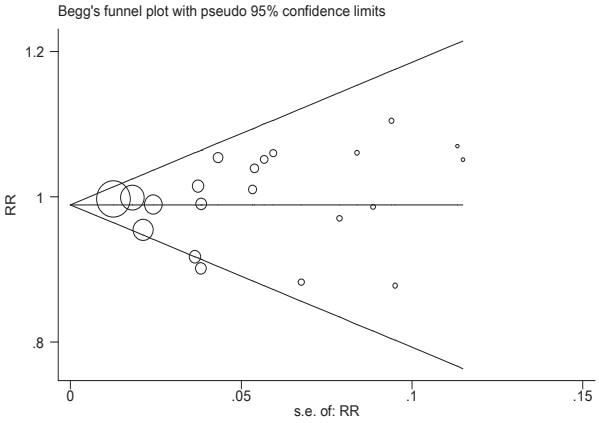

Figure 3. Begg's Funnel plot for evaluation of publication bias.

($P < 0.05$).

The results of a similar study conducted by Feng et al in 2010 (41) have shown no significant relationship between gene 308 G/A polymorphism TNF-α and T2DM.

In this study we added the result of four conducted studies from 2010 to 2013 to the result of study performed by Feng et al. In his another work, Feng shows that the high levels of polymorphism 308 G/A allele of TNF-α gene is a risk factor for diabetes type 1 (42). In a research by Furuta et al carried in Japan on 308 G/A, 132 diabetic patients and 142 healthy controls, the association between single nucleotide polymorphisms in the TNF-α gene promoter region was found in diabetic patients and controls (24).

Mukhopadhyaya et al, in a work performed by the Indian population of 40 diabetic patients and 40 control subjects have found an association between single nucleotide polymorphisms in the promoter region of genes 308-G/A TNF-α and T2DM (43).

Costa et al evaluated 36 patients with diabetes and 41 control subjects. Low 863 G/A TNF-α allele and a high concentration of soluble receptor-2 (TNFR2) TNF-α were associated with the higher incidence of diabetes type 2. This article has shown that there is an abnormal increase of TNF-α disease, which is closely related to genetics, metabolism and indicated T2DM indexes (44). This meta-analysis study aimed to investigate the association between polymorphisms in G/A 308 gene TNF-α and metabolic syndrome. The findings demonstrate that allele A–TNF increases the risk of metabolic syndrome (45). Additionally, in another study, a significant association between increased body mass index and polymorphisms has been reported in Swedish women (29).

In a meta-analysis conducted on Han Chinese population, 10 studies including 1425 diabetic patients and 1116 healthy controls were studied. The results have shown that A<G-308 polymorphism is a major risk factor for T2DM and at the locus of A allele may be critical for the development of T2DM in the Han Chinese population (46). Results have shown that in other races, including the Whites (27,28,33) and Japanese (24,30) polymorphism A<G 308 TNF-α is not a risk factor for the development of T2DM. Hence, it is concluded that the race of the subjects is an important factor in making final conclusion.

According to previous studies conducted in different populations, the overall conclusion of this study was that there was no significant association between allelic sequences in 308 G/A gene for tumor necrosis factor-alpha (TNF-α) and the risk of T2DM. However, T2DM and insulin resistance is multi-factorial disorders in which diverse genetic locus susceptibility involved in disease occurrence. Environmental factors (such as nutrition and physical activity) are also, effective in development of this phenotypic occurrence (47). Besides, other factors such as obesity, lack of physical activity and diet are involved in the development of such disease (48). In general, the result of TNF-α gene polymorphism and T2DM is inconsistent. Depending on the population studied, it shows various effects (11). Here, we should remind that populations with a high incidence of T2DM are widespread, for example in the Pima Indian population that cannot be dedicated to environmental factors (49).

5. Conclusions

In general, it is suggested that we need to have in future

research, not only to recruit more samples but also focus on environmental factors such as ethnic differences.

Authors' contribution

AHD and MZA; The concept, design, data analysis, and manuscript preparation and final revision. MD, FK and MRT; performing search, data collection, data extraction and writing proposal. AHD and KS; statistical analysis, manuscript editing, and manuscript review. MZA; data collection and providing first draft and submission.

Conflicts of interest

The authors declare that they have no conflict of interest regarding the contents of this article.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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