Association between -308G/A TNFA Polymorphism and Susceptibility to Type 2 Diabetes Mellitus: A Systematic Review

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Diabetes mellitus (DM) is considered to be a worldwide epidemic disease and its type 2 form comprises more than 95% of all cases. Tumor necrosis factor-alpha (TNF-α) is a proinflammatory cytokine. Its dysregulation has been implicated in a variety of human diseases, including type 2 diabetes mellitus (T2DM). The control of expression of this cytokine is associated with insulin resistance and has a strong genetic influence. In order to understand this relationship, the literature from all case-control studies since 2000 to date was reviewed. The genotypes frequency results presented in ten publications with different ethnicities were compared. The correlation between the TNFA promoter genotypes and the risk of developing T2DM remains controversial due to the many discrepancies between the different studies available. Ethnic differences may play a role in these conflicting results, since the distribution of TNFA promoter polymorphisms is distinctive between individuals of dissimilar racial origin. Hence, although the relationship between T2DM incidence and presence of polymorphisms at position -308 of the TNFA gene is not entirely clear, the results of these studies suggest the need for further investigation.

1. Introduction

Noncommunicable diseases, including type 2 diabetes mellitus (T2DM), are considered the leading cause of death in the world and, in Brazil, constitute the main cause of diseases. T2DM assumes an important role in this context given that it is considered a worldwide epidemic disease; in 2011 it appeared among the ten leading causes of death in the world and it is prospected that number of cases will continue to increase [1]. The increase in prevalence is due to several factors. The ones most frequently being discussed are the increase in population life expectancy, changes in lifestyle (including unbalanced diet and physical inactivity), and obesity [2].

Diabetes can be defined as a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The underlining cause of T2DM can be attributed to a combination of resistance to the action of the hormone, increased production of insulin in a compensatory manner, and inadequate secretory response [3].

On the other hand, according to a study conducted by Kaprio et al. [4], the heredity has an input around 47% in susceptibility to T2DM; thus, genetic factors play an important role in the development of the pathology [5]. Some facts corroborate the importance of heritability in T2DM: the greater concordance between monozygotic twins than among dizygotics twins and a wide variation in the prevalence of T2DM in epidemiological studies with different ethnic groups as well as positive results in numerous other genetic studies [6]. In this regard, it should be noted that even as more than 30 genes associated with T2DM have been identified, the contribution of each individual gene in the disease susceptibility is very small [7]. Additionally, most of these genes identified are related to dysfunction of pancreatic β cells [7].

Several reports suggest that the characteristics of each individual, including genetic polymorphisms, may confer differences in the occurrence of diabetes and other complex
diseases such as cancer and heart disease [8]. The number of
genesis tested for the predisposition to T2DM is huge. Withal,
in most cases, a positive association between polymorphisms of
these genes and T2DM are not reproducible in the analysis of
a different population [9]. One of these genes is TNFA that
codes the TNF-α protein. This molecule is composed of
157 amino acids located on chromosome 6. This cytokine is
involved in inflammation, apoptosis, infections, and cancer
processes [10]. Two polymorphisms in the promoter region of
the TNFA gene have been described, one present at position
-308 [11]. In this regard, Swaroop et al. [12] demonstrated an
association between the adipocytokine TNF-α and development
of insulin resistance.

This systematic review was conducted to provide a
comprehensive assessment of the association between the
polymorphism in the gene TNFA -308G/A and the presence
of T2DM.

2. Material and Methods

2.1. Search Strategy. The literature search was made through
the Virtual Health Library (VHL) which uses as bibliographic
databases the publications found in sources such as
LILACS, MEDLINE, and other information bases such as
open educational resources, websites, and scientific events.
Any publications with case-control studies, on January 21,
2016, that show the relationship between polymorphisms of
TNFA gene -308G/A and susceptibility to type 2 diabetes
mellitus (T2DM) were surveyed. The search terms used were
as follows: “diabetes” and “TNF” or “tumor necrosis factor”,
and “polymorphism”. The items recovered were then selected
to be studied focusing on T2DM. There was no language
restriction placed in the literature searched.

2.2. The Filters and Inclusion and Exclusion Criteria. The
filters are selected in accordance with the main subjects
of the following terms: “type 2 diabetes mellitus”, “tumor
necrosis factor alpha”, “single nucleotide polymorphism”,
and “genetic polymorphism”. The filter base on the type of
study included solely the term “case-control study”. Inclusion
criteria were as follows: (1) the study must have been case-
control; (2) the study should have assessed type 2 diabetes
mellitus and -308G/A polymorphism of TNFA gene, even if
associated with other comorbidities; and (3) the study should
have provided sufficient data, including the number or fre-
cquency of alleles and genotypes. Studies were excluded if (1)
there were commentaries, case reports, or non-case-control
or meta-analyses studies; (2) they did not report sufficient
data; (3) they presented data from other types of diabetes or
did not specify what kind patients had; and (4) they showed
polymorphism in another coding region of the TNFA gene or
(5) if the sample was composed of only DM patients.

2.3. Data Extraction. Data from eligible studies were extract-
ed independently in accordance with the inclusion and exclu-
sion criteria. For each study the following characteristics were
collected: the authors, the study title, the year of publication,
where it was published, the sample size, the TNFA -308G/A
genotypes with their corresponding simple frequencies and
percentages for the control and the case group, and the
study’s $p$ value and odds ratio, when calculated.

3. Results

3.1. Study Characteristics. The literature search found articles
published starting from 2000, given that the year the complete
mapping of the human genome was made available. Advances
in molecular biology technology since this project have been
quick and, thus, increasing the number of genetic studies
published for the association of certain genetic polymor-
phisms with various pathologies.

In the case of literature search for articles with case studies
that related polymorphism position -308 of the TNFA gene
with diabetes, the result presented forty-three publications
between the years 2003 and 2015, ten of which met the criteria
inclusion.

Thirteen studies presented results for other types of dia-
betes; eleven related to type 1 diabetes and two to gestational
diabetes. Two others did not specify what type of diabetes
had patients in the case group. Two of these studies did not
show enough genetic data for analysis. In relation to TNFA
gene, seven studies presented polymorphisms in region other
than the -308 position and three publications had single
nucleotide polymorphism in a gene that was not TNFA.
Other studies were excluded due to different methodological
designs in their inclusion criteria: two meta-analysis, one
being observational and the other prospective and, relative
to the sample. Furthermore, there was a publication that
presented data of diabetic patient’s polymorphisms in both
the control and the case group.

Finally, a total of ten articles were included in this sys-
tematic review. The number and homogeneity of the included
studies presented were too limited to allow a meta-analysis.

Two studies (Vendrell et al. [11], Garg et al. [18]) relate
the polymorphism in gene studied with T2DM and coronary
heart disease, while another two (Buraczynska et al. [14],
Dabhi and Mistry [21]) relate it with obese T2DM patients
in question with T2DM (Shiau et al. [13], Bouhaha et al. [15],
Guzmán-Flores et al. [16], Saxena et al. [19], and Sefri et al.
[20]), one of which also relates it with obese T2DM patients
(Bouhaha et al. [15]). The general characteristics of the studies
included in this review are summarized in Table 1.

3.2. Results of the Systematic Review. In three studies con-
ducted in Spain, Hungary, and Morocco significant associa-
tions between the TNFA -308G/A polymorphism and the risk
of T2DM were identified [11, 17, 20]; two of these in patients
with other comorbidities such as coronary heart disease [11]
and atherosclerosis [17].

In the present study, therefore, we infer that although
there was no evidence of heterogeneity in the association
between polymorphisms in the TNFA -308G/A gene and
increased risk for development of T2DM, the presence of
positive results may mean that few studies have not been
Table 1: Comparison of type 2 diabetes mellitus case-control study results for the -308 TNFA gene.

<table>
<thead>
<tr>
<th>Author</th>
<th>Study</th>
<th>Year</th>
<th>Country/Ethnicity</th>
<th>Sample</th>
<th>TNFA -308 polymorphism</th>
<th>Case group frequency</th>
<th>Control group frequency</th>
<th>p value</th>
<th>Odds ratio (in article)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vendrell et al. [11]</td>
<td>A polymorphism in the promoter of the tumor necrosis factor-α gene (-308) is associated with coronary heart disease in type 2 diabetic patients</td>
<td>2002</td>
<td>Spain n = 313</td>
<td>GG</td>
<td>63 (59.4%)</td>
<td>159 (76.8%)</td>
<td>48 (23.2%)</td>
<td>p = 0.41 OR = 0.75</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>GA + AA</td>
<td>43 (40.6%)</td>
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<tr>
<td>Shian et al. [13]</td>
<td>TNF-α polymorphisms and type 2 diabetes mellitus in Taiwanese patients</td>
<td>2003</td>
<td>Taiwan n = 444</td>
<td>GG</td>
<td>218 (84.82%)</td>
<td>168 (89.84%)</td>
<td>16 (8.56%)</td>
<td>p = 0.2343</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>GA</td>
<td>35 (13.62%)</td>
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<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>AA</td>
<td>4 (1.56%)</td>
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<tr>
<td>Buraczynska et al. [14]</td>
<td>Genetic determination of TNF and myeloperoxidase production in dialed patients with diabetic nephropathy</td>
<td>2004</td>
<td>Poland n = 210</td>
<td>TNF1/TNF2 (GG)</td>
<td>22 (59.5%)</td>
<td>Healthy 86 (74.8%)</td>
<td>Other nephropathy 40 (69%) (case versus control -healthy)</td>
<td>p = 0.07</td>
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<td></td>
<td>TNF1/TNF2 (GA)</td>
<td>13 (35.1%)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>TNF1/TNF2 (AA)</td>
<td>2 (5.4%)</td>
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<tr>
<td>Bouhaha et al. [15]</td>
<td>Study of TNF-α -308G/A and IL-1βG/C polymorphisms in type 2 diabetes and obesity risk in the Tunisian population</td>
<td>2010</td>
<td>Tunisia n = 494</td>
<td>GG</td>
<td>141 (72.3%)</td>
<td>204 (68.2%)</td>
<td>89 (29.7%)</td>
<td>p = 0.34</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>GA</td>
<td>51 (26.1%)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>AA</td>
<td>3 (1.6%)</td>
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<tr>
<td>Guzmán-Flores et al. [16]</td>
<td>Tumor necrosis factor-alpha gene promoter -308G/A and -238G/A polymorphisms in Mexican patients with type 2 diabetes mellitus</td>
<td>2011</td>
<td>Mexico n = 904</td>
<td>GG</td>
<td>225 (86.9%)</td>
<td>573 (88.8%)</td>
<td>69 (10.7%)</td>
<td>p = 0.558 (GG versus GA)</td>
<td>OR = 1.14</td>
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<td></td>
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<td></td>
<td></td>
<td>GA</td>
<td>31 (12.0%)</td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>AA</td>
<td>3 (1.1%)</td>
<td></td>
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<tr>
<td>Szabó and Acádiy [17]</td>
<td>Tumor necrosis factor-α -308 GA polymorphism in Atherosclerotic patients</td>
<td>2011</td>
<td>Hungary n = 314</td>
<td>GG</td>
<td>DM + AVE 40 (61.6%)</td>
<td>141 (76.7%)</td>
<td>(control versus DM + MI)</td>
<td>p &lt; 0.05 (control versus DM + AVE)</td>
<td>OR = 0.71</td>
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<td></td>
<td>GA</td>
<td>20 (30.7%)</td>
<td></td>
<td>(control versus DM + AVE)</td>
<td>p = 0.005</td>
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<td></td>
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<td></td>
<td></td>
<td>AA</td>
<td>5 (7.7%)</td>
<td></td>
<td>(control versus DM + AVE)</td>
<td>p = 0.005</td>
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<td></td>
<td>6 (9.2%)</td>
<td></td>
<td>(control versus DM + AVE)</td>
<td>p = 0.005</td>
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</tr>
<tr>
<td>Garg et al. [18]</td>
<td>Prominantly cytokine gene polymorphisms and threat for coronary heart disease in a North Indian Agrawal population</td>
<td>2012</td>
<td>Indian n = 322</td>
<td>GG</td>
<td>117 (85.4%)</td>
<td>146 (78.9%)</td>
<td>40 (20.54%)</td>
<td>p = 0.27</td>
<td>OR = 0.18 (GA/AA versus GG)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>GA</td>
<td>20 (14.59%)</td>
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<td></td>
<td></td>
<td></td>
<td>AA</td>
<td>0</td>
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<tr>
<td>Saxena et al. [19]</td>
<td>Association of IL-6, TNF-α, and IL-10 gene polymorphisms with type 2 diabetes mellitus</td>
<td>2013</td>
<td>Indian n = 353</td>
<td>GG</td>
<td>173 (81.2%)</td>
<td>111 (79.3%)</td>
<td>(allele G versus A)</td>
<td>p = 0.3766</td>
<td>OR = 1.07 (allele G versus A)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>GA</td>
<td>33 (15.5%)</td>
<td>25 (17.9%)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>AA</td>
<td>7 (3.3%)</td>
<td>4 (2.9%)</td>
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<tr>
<td>Sefri et al. [20]</td>
<td>TNFA -308G/A polymorphism in Moroccan patients with type 2 diabetes mellitus: a case-control study and meta-analysis</td>
<td>2014</td>
<td>Morocco n = 551</td>
<td>GG</td>
<td>38 (42.38%)</td>
<td>60 (24.59%)</td>
<td>(allele G versus A)</td>
<td>p = 0.000002</td>
<td>OR = 1.79 (allele G versus A)</td>
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<td></td>
<td></td>
<td></td>
<td>GA</td>
<td>154 (50.16%)</td>
<td>133 (54.51%)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>AA</td>
<td>115 (37.56%)</td>
<td>51 (20.90%)</td>
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<tr>
<td>Dabhi and Mistry [21]</td>
<td>Oxidative stress and its association with TNF-α -308G/C and IL-1α -889C/T gene polymorphisms in patients with diabetes and diabetic nephropathy</td>
<td>2015</td>
<td>Indian n = 449</td>
<td>GG</td>
<td>185 (86.40%)</td>
<td>191 (81.11%)</td>
<td>0</td>
<td>p = 0.41</td>
<td>OR = 0.75</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>GA</td>
<td>27 (12.62%)</td>
<td>44 (18.88%)</td>
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<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>AA</td>
<td>2 (0.97%)</td>
<td>0</td>
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</tr>
</tbody>
</table>

* p < 0.005.
enough to clarify this relationship, and besides there is no
documented evidence in various ethnic groups. Due to con-
tradictory results, this systematic review is aimed at providing
a comprehensive assessment of the association between
TNFA -308G/A and phenotype involving type 2 diabetes.

4. Discussion

The concern regarding the quantification and qualification of
the genetic impact on phenotypic characteristics started after
the first complete human sequence after genomic era [22].

As a consequence, health research delved into the genetic
information as a way to find answers to complex disease
questions. This type of research has shown high prevalence
and increasing prospects in a number of cases, such as
diabetes [23]. For this purpose, various portions of the human
gene are now analyzed in search for genetic variations
among individuals that could explain these diseases. Studies
seeking interactions between these variations, in particular,
have been very promising [24].

In the case of diabetes, a syndrome whose etiology is
complicated and involves several risk factors for its devel-
opedment and progression, some studies on single nucleotide
polymorphisms were suggested as causing the phenotypic
characteristics and responsible for the increased risk of
developing pathology [25–27].

To study the risk factors for a disease is to study the
possibility of a certain event happening. Within the epidemi-
ological concepts, the term is used to predict the likelihood
of healthy individuals, exposed to certain factors, developing
a given disease. This does not necessarily mean that it would
occur; nevertheless the presence of these factors makes the
individual more vulnerable to manifest the disease. A risk
factor “x” may be the trigger of various diseases, and several
risk factors can cooperate for the genesis of a common disease
[28].

Environmental factors such as eating habits [29–31] and
physical inactivity [32–34], in addition to the concomitant
presence of diverse mutations in many genes, need to be
considered so that the contribution of each of them is
understood.

There are two types of genetic epidemiological studies:
linkage studies and association. Linkage research studies
gene-
carriers and specific polymorphisms in a family
that has the disease. This, thus, allows the researchers
a way to better study the regions of a chromosome that is
affected. After the connection is made to the chromosome,
one can test for association of polymorphisms for identifying
a genotype specific to a given disease in groups of people who
have the targeted disease [34, 35].

Several association studies have discussed the importance
of clarifying the relationship between genetic polymorphisms
and the development of type 2 diabetes.

The search for candidate genes was initially focused on
possible genes encoding proteins directly involved in the
pathophysiology of T2DM: related encoders, for example,
production, secretion or activity of insulin, or development
of the pancreas [36–38].

Gradually, however, emerging studies suggested that sev-
eral other factors could contribute to the development of
T2DM, as the expression of proinflammatory cytokines and
other molecules that act in the inflammatory process and that
appear to play a critical role in the development of chronic
complications of DM [39]. Several studies have shown the
influence of various polymorphisms in proinflammatory
cytokines genes as a risk of development of obesity, diabetes,
and metabolic syndrome [40]. One of these cytokines, tumor
necrosis factor (TNF-α), has been investigated since diabetics
have elevated levels of it circulating. TNF-α has also been
implicated as an insulin resistance-causing factor associated
with the pathogenesis of T2DM [41].

TNF-α is a proinflammatory cytokine that acts in the
regulation of cell proliferation, differentiation, and apoptosis
[42]. Among the various polymorphisms describing the
TNFA gene, the -308G>A variant located in the promoter
region excels by affecting the expression of its gene [43]. The
presence of the A allele at nucleotide -308 increases transcrip-
tion of TNFA gene approximately twofold, therefore increas-
ing the production of this cytokine [44]. Under this circum-
stance, it is expected that the polymorphic genotype may be
associated with an increased frequency of diabetes and, for
the proper association, of case-control studies can be used.

In this review, several studies with the frequency of
genotypes in control and case group were observed for a
better understanding of the population genetic profile and a
possible association between polymorphism of TNFA gene
and T2DM in groups with different ethnicities. The influence
of genetic polymorphisms on certain diseases may be found
in a population and yet not in another; this may impact
the frequencies and distribution of a given polymorphism
in distinct population. The difference in influence may be
due to racial variation as well as other factors. [45]. In
addition, some studies have included a proportionally small
sample size in relation to the country’s population and most
of them define the case of groups in T2DM patients who have
concomitant comorbidities.

Case-control studies were selected in this review and
were made with the people of Spain, Taiwan, Poland, India,
Tunisia, Mexico, Hungary, and Morocco; nonetheless a pos-
itive association was only found in the Spanish, Hungarian,
and Moroccan population.

Sefri et al. [20] in their meta-analysis, which considers
21 case-control studies published until August 2013, argue
that no significant associations were found between the
polymorphism in the studied region of the TNFA gene
and risk of developing T2DM. Their finding was consistent
with a previous meta-analysis, which included data from 18
association studies [46]. In these studies, publications with
different ethnic groups were included; among them were
Africans, Asians, Caucasians, and other populations.

So, when comparing the frequencies of polymorphic
genotypes (GA and AA) in the groups of case-control study
(described in Table 1), it is possible to observe that these
genotypes are presented more frequently in the group that
has the disease. The exceptions to this were the studies in
Tunisia and India; the most frequent genotype in type 2
diabetic patients was the GG. In all other countries there
was an increase of polymorphic genotype in T2DM group. This evidence supports the assumption that polymorphisms in the TNFA gene and its association with other aspects, both genetic and environmental, may represent an important risk factor for type 2 diabetes mellitus.

5. Conclusion

Risk factors for T2DM are increasingly more prevalent in the population. Risk factors not modifiable or irreversible in nature, such as genetic profiles, refer to the individual characteristics. Even though these factors may not be changed, the identification of their presence in individuals and families may enable health professionals to advise change in the lifestyle of these patients, avoiding early manifestation of T2DM.

Competing Interests

The authors declare that there is no conflict of interests regarding the publication of this article.

References


