Review

Interleukins Polymorphisms In Type-1 Diabetes And Periodontitis: A Review

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Review

Interleukins Polymorphisms in Type-1 Diabetes and Perio-Dontitis: A Review

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Abstract: Diabetes may cause an increase blood levels of cytokines inducing a rising of C reactive protein (PCR) and fibrinogen stimulating a subclinical inflammation which lead to adhesive molecules expression and to endothelial disfunction. A comprehensive panel of type 1 diabetes mellitus (T1DM) interleukins polymorphisms is not provided yet. As chronic periodontitis (CP) is considered the sixth complication of DM, a clarification is needed about the inflammatory role managed by single nucleotides polymorphisms (SNPs). The goal of this review is to focus on the significant diversity of SNPs in T1DM patients with and without CP. After a digital search on PubMed and Scopus with reference to the last 5 years, 21 items were enrolled. Several ILs were analyzed. T1DM still needs to be thoroughly explored regarding the ILs polymorphisms panel, however the last 5 years have led to the increased independence of this condition, causing autonomous inflammatory effects which requires further investigations. CP and T1DM association in children and adolescents represents a severe gap in literature that should be filled, the scarce presence of studies also about adults serves as a motivation for ulterior clinical researches

Keywords: type 1 diabetes; polymorphisms; interleukins; periodontitis; systemic inflammation; peripheral inflammation; childhood

1. Introduction

Type 1 diabetes mellitus (T1DM) is a complex autoimmune disease with genetic implications defined by a T-cell mediated destruction of pancreatic β cells leading to uncontrolled hyperglycemia and insulin-dependence [1]. It occurs mainly in childhood and adolescence, although cases in adulthood are not so uncommon, and it is known as Latent Autoimmune Diabetes [2]. People with LADA may have a residual β cells function, and diabetes onset could be slow and free of insulin dependence for years after the diagnosis.

We can recognize two different groups, one represented by Autoimmune Diabetes Mellitus: the first one is caused by beta cells destruction by antibodies, that mostly affects subjects in their infancy and adolescence. The other group is represented by Asian and African ethnicity, with a still controversial pathogenesis, the presence of hyper-glycemia but no autoimmune evidence.

The development of T1DM is the result of an elaborate interplay of multiple genetic and environmental factors are still poorly recognized, although evidence seems to point out that the environment plays a role in T1DM expression, as it is demonstrated from different expressions in genetically similar populations [3].

In fact, chronic low-grade inflammation and environmental factors seem to play a crucial role in the development of this pathology.

In 2021, T1DM involved 8.4 million individuals, of these 18% (1.5 million) were younger than 20 years [4].

Human leukocyte antigen (HLA) class II genes have been proven to play a relevant role in defining a relevant risk to develop T1DM [5].

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Interleukin-1α (IL-1α), a well-known pro-inflammatory cytokine, plays a relevant role in immune response and inflammatory regulation. For this reason, single nucleotides polymorphisms (SNPs) could lead to different proteins with an influence on the immune response and, subsequently, with measures of glucose homeostasis and diabetes [6].

Recent advances in research highlighted that patients affected by T1DM have an altered Interleukin expression.

Chronic Periodontitis (CP), a pathology characterized by progressive loss of periodontal attachment and subsequent tooth loss have been demonstrated to be in tight conjunction with DM. as this could be considered the sixth complication of DM [7].

Although systemic low-grade inflammation, as an expression of IL polymorphism, seems to play a role in Chronic Periodontitis (CP) development, few studies in literature have investigated this aspect in the last years.

In the recent past, few studies have been conducted to assess if IL polymorphism could be considered a preventive measure to assess the risk of developing CP or its evolution. One of these evaluated the presence of IL-1 SNPs in association with the presence of other risk factors in order to stratify population in different range of risk to develop CP and evaluate the effectiveness of preventive care. Aim of that paper was to assess where resources for preventive treatments should be better targeted to achieve the better results in terms of prevention and care. [8]

On the other hand, a recent study about the relation of IL-8 polymorphism and CP revealed that although the relation between IL-8 and DM is clearly assessed, in the evaluated sample the relation between the circulation of periodontal bacteria and circulating IL-8 was not confirmed. Therefore, the relationship between CP and IL-8 polymorphism, although advocated, was not validated [9]. In another study, although a relation between IL-17 and T1DM control and "red complex" occurrence in both diabetic patients with CP and patient with CP, at the same time the principal limit of the study was related to the relatively low number of the sample [10]. Aim of the present study is to evaluate the relationship between IL polymorphism, T1DM and CP.

2. Materials and Methods

A systematic review was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews and meta-analysis [11] and registered on PROSPERO - International prospective register of systematic reviews – with ID code CRD42022358862 [12].

Literature Search

To identify relevant studies investigating the linking between T1DM and interleukins polymorphisms, a comprehensive search of PubMed and Scopus, using the Patient/Population/Problem, Intervention, Comparison and Outcome (PICO) format, was conducted regarding the last 5 years.

- Population: humans and animals;
- Intervention: interleukins polymorphisms in healthy subjects;
- Comparator: interleukins polymorphisms in T1DM patients/animals;
- Outcomes: correlation between interleukins polymorphisms and T1DM.

The following MeSH were used: "interleukins polymorphisms type 1 diabetes mellitus", "and periodontitis".

Eligibility Criteria

The inclusion criteria were as follows: all studies analyzing the variety of polymorphisms among interleukins linked with T1DM, in humans and animals.

The exclusion criteria were as follows: research about polymorphisms of other cytokines; papers about the linking between interleukins and other pathological conditions; systematic reviews; metanalyses; editorials; abstracts.

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Data Extraction

Studies were screened by two reviewers independently, and a matrix of relevant data was produced. Disagreements were resolved by consensus with a third reviewer. Data extraction included general details relating the characteristics of the studies (e.g., author, year of publication, sources of funding) and specific details about the type of interleukins and their polymorphisms.

Assessment of Methodological Quality

The methodological quality of included studies was assessed using the prediction model risk of bias assessment tool Newcastle-Ottawa Quality Assessment Scale (Table A1). A qualitative description of the characteristics of the included studies as well as a narrative data synthesis was performed.

3. Results

3.1. Overall Scenario

The initial search provided a total of 277 items; in detail 32 from PubMed and 245 from Scopus. No paper was removed because ineligible by automation tools, while 25 records were removed for other reasons, for example, for the study of other diseases in addiction of diabetes, or for the analyses of other cytokines. 252 articles accessed the screening phase, and a total of 205 items were removed because of lack of interest in shown data (202) or because represented a systematic review with or without metanalysis (3). Eligibility was assigned to 47 records from which 16 were removed for being duplicates, 9 for being abstracts and 1 for being an editorial. Finally, a total of 21 papers were involved for the inclusion phase (Figure 1).

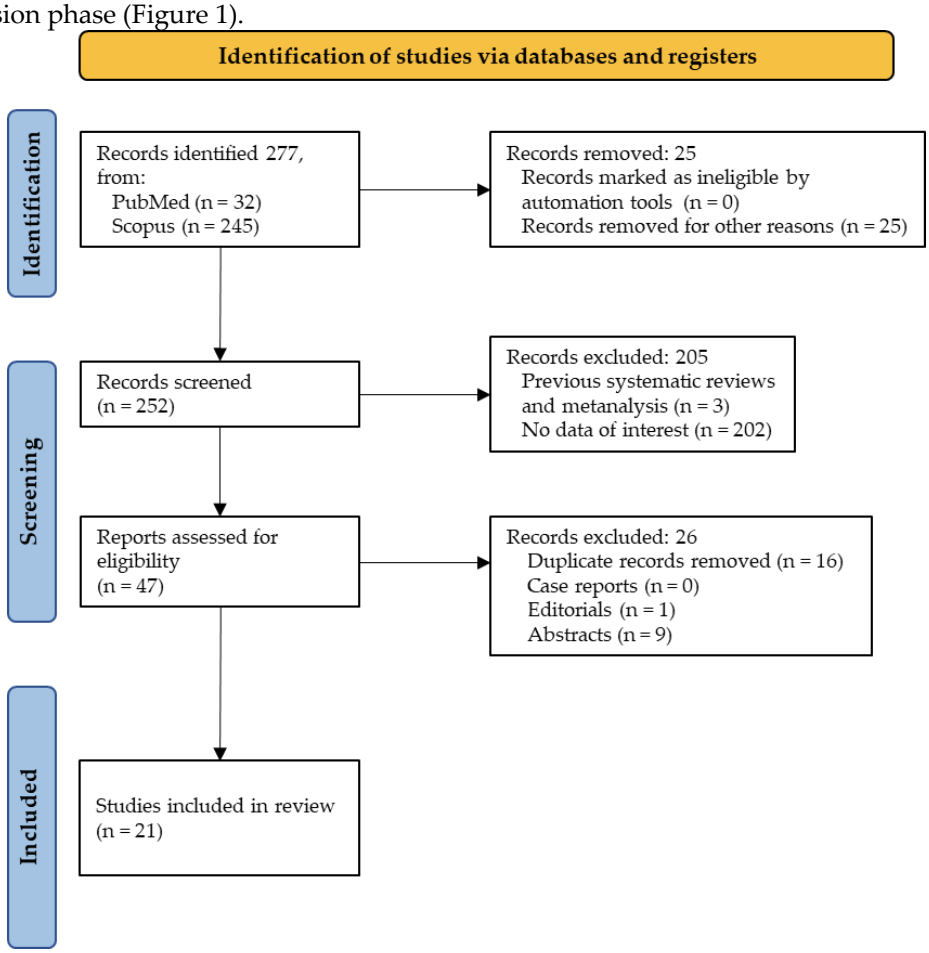

Figure 1. PRISMA flowchart.

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A detailed table was drawn up including each eligible article, authors, year, population, nationality, type of sample, interleukin, polymorphism (Table 1). A brief narrative summary is shown in Table A2.

Table 1. Keys results. Children up to 10 years. Adolescents up to 18 years. Adults from 18 years and over. NGS, Next Generation Sequencing. PCR, Polymerase Chain Reaction. sIL-2R, soluble IL-2 receptor. IL-2RA, IL-2 Receptor Alpha.

Authors/Year	Population (Age)/Ethnicity	IL/#Polymorphism	Analysis
Hoffman M. et al. 2022 [13]	349 (Children/adolescents)/German	IL-7/2	NGS
Li J. et al. 2022 [14]	270 (Adults)/Chinese	IL-6, IL-17(A-F)/7	PCR
Osman A. E. et al. 2022 [15]	371 (All ages)/Saudi	IL-4, IL-10/5	PCR
Ali Y. et al. 2021 [16]	218 (Children)/Egyptian	IL-6, IL-18/3	PCR
El Helaly R.M. et al. 2021 [17]	230 (Children/adolescents)/Egyptian	IL-10/2	PCR
Haghnazari L. et al. 2021 [18]	136 (Adults)/Iranian	IL-6/1	Spectrophotometry
Hehenkamp P. et al. 2021 [19]	40 (Children)/German	IL-7/1	PCR
*Kumar S. et al. 2021 [20]	90 (Adults)/Indian	IL-17A/1	PCR
Li J. et al. 2021 [21]	1092 (Adolescents)/Chinese	IL-1B/2	Mass spectometry
Osman A. E. et al. 2021 [22]	328 (All ages)/Saudi	IL-1(A, B), IL-2, IL-12/5	PCR
Tangjittipokin W. et al. 2021 [23]	200 (Children/Adolescents)/Thai	IL-2, IL-4. IL-6, IL-10, IL-13, IL-17A/6	PCR
Campos L. P. et al. 2020 [24]	611 (Children/Adults)/Euro-Brazilian	IL-18/1	PCR
Keindl M. et al. 2020 [25]	79 (Adults)/Scandinavian	sIL-2R/68	Flow citometry
Sharma C. et al. 2020 [26]	310 (Adolescents, Adults)/Emiratis	IL-2RA/1	PCR
Boechat-Fernandes A. et al. 2019 [27]	1101 (Adolescents)/Brazilian	IL-12B, IL-18/3	PCR
*Borilova Linhartova P. et al. 2019 [28]	659 (Adults)/Czech	IL-1/2	PCR
Campos L. P. et al. 2019 [29]	291 (Adults)/Euro-Brazilian	IL-6, IL-6R/2	PCR
Lundtoft C. et al. 2019 [30]	301 (Children, Adolescents)/German	IL-7RA/2	PCR
*Borilova Linhartova P. et al. 2018 [9]	109 (Adults)/Czech	IL-8, IL-8R/2	PCR
Seyfarth J. et al. 2018 [31]	301 (Adolescents)/German	IL-7RA, sIL-7R/2	PCR
Al-Lahham Y. et al. 2017 [32]	280 (Adults)/Euro-Brazilian	IL-18/1	PCR

* Articles considering periodontitis.

3.2. Detailed Results

None of the included articles concerned animals. Regarding the population age 38.1% (8/21) of items refers to adults, 23.8% (5/21) refers to children and adolescents, 14.3% (3/21) refers to

adolescents, 9.5% (2/21) refers to children, 9.5% (2/21) refers to all ages and finally 4.8% (1/21) refers to children and adults. As concerns ethnicity the most investigated was the German population in 19% (4/21) of studies, followed by the Euro-Brazilian people in 14.3% (3/21) of studies. Other ethnic groups such as Chinese, Saudi, Egyptian and Czech appeared each in 9.5% (2/21) of reports. The least investigated cluster were Iranian, Indian, Thai, Scandinavian, Emiratis and Brazilian in 4.8% (1/21) of cases. Interleukins analyzed in descending order were IL-6, IL-2, IL-7, IL-1, IL-10, IL-17, IL-4, IL-8, IL-18 and finally IL-12. The most used technique to examine these specific cytokines was the Polymerase Chain Reaction (PCR), more rarely the Next Generation Sequencing (NGS), spectrophotometry, mass spectometry and flow citometry. All included studies used peripheral blood samples to perform these tests. Only 14.3% (3/21) of items discusses about periodontitis.

4. Discussion

A systematic review following the PRISMA flowchart was performed in order to assess the state-of-the-art about the relationship between ILs SNPs and T1DM, furthermore the link with periodontitis was investigated as well. Due to a considerable heterogeneity in polymorphisms regions and among several interleukins' measures, a formal meta-analysis was not carried out.

IL-1 and its SNPs were investigated by Li J. et al. [21], more specifically authors established that the concentration of IL-1β in T1DM patients was significantly higher than that in healthy controls. Tangjittipokin W. et al. [23] assessed that IL1B SNPs are associated with T1DM susceptibility.

IL2RA gene variants might increase the risk of developing vascular complications in people with T1DM [25] and could confer risk alleles for T1D among the Emirati population [26].

Osman A. E. et al. [22] found out ILs (IL-1A/B, IL-2, IL-12) levels in T1DM were higher than controls.

The SNP associated with low production of IL-4 increases the risk of T1DM in young individuals carrying vulnerable HLA alleles/haplotypes [15].

IL-6 was well investigated by Haghnazari L. et al. [18], assessing that the G allele of SNP rs1042522 encoding the TP53 gene for IL-6 increases the risk of developing DM in Iranian population. At the same time, IL-6R rs2228145 was associated with T1D develoment in adulthood [29].

SNPs for IL-7 in T1DM patients was investigated in several valuable works [13,19,30,31]. Hoffman M. et al. [13] revealed a higher sIL-7R serum concentrations at T1DM onset and decreasing levels during therapy, whereas IL-7 was only higher in long term patients as compared to controls. Hehenkamp P. et al. [19] elucidated that T1DM monocytes have impaired IL-7 response and lower IL-7R expression. According to Lundtoft C. et al. [30] IL-7Rα variants may contribute to disease susceptibility against T1D. Finally, Seyfarth J. et al. [31] pointed out that only T1DM children with the protective haplotype had lower IL-7 serum levels.

Regarding IL-10, El Helaly R.M. et al. [17] stated that AA genotype and A allele of IL-10 rs1518111 SNP could be linked to increased risk for T1DM among Egyptian children.

With reference to IL-17, increased serum IL-17A is a risk factor for autoimmune T1DM [14].

Finally, IL-18 has a controversial role because the IL-18 gene promoter polymorphisms might be associated with susceptibility to T1DM in Egyptian children [16] and with T1DM age onset [27], but at the same time according to Campos L. P. et al. [24] IL-18 polymorphisms were not associated with T1DM onset in children or adults in this population, along with Al-Lahham Y. et al. [32], according to which IL-18 rs187238 was not associated with T1DM in Euro-Brazilian population.

The burden of CP is investigated only in few studies in the present review. In particular, Kumar S. et al. [20] found out that IL-17A polymorphism was not associated with increased risk for CP in T1DM patients. In a similar way, Borilova Linhartova P. et al. [28] considered the variability in the IL-1B and IL-1RN genes as possible factor in the susceptibility to T1DM and CP, although the single variants of these polymorphisms are not crucial for the protein production. The same authors also explored the IL-8 role, concluding that CP does not influence the circulating IL-8 levels and that patients with T1DM and CP had higher circulating IL-8 levels than healthy controls with CP and non-periodontitis subjects [9]. It has to be stressed that all of these studies about CP referred to adults, while childhood and adolescence seemed to be left out.

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Limitations of the Study

A crucial factor of our review was the challenge to overcome studies heterogeneity in terms of methods of interleukin analysis and direct or indirect correlation of T1DM and its complications. Sometimes authors left out the specific technique of analysis creating an important bias that must be kept in mind. Finally, other confounding factors were represented by the existence of several polymorphisms' detection for the same interleukin.

5. Conclusions

To the best of our knowledge, ILs SNPs still represents a controversial field in the understanding of the inflammation aspects in T1DM. Most of the studies analyzed pointed out how a higher ILs concentration is present in this specific population, but an univocal explanation about the genetic characterization is not completely available.

It seems that CP is an adjunctive factor for the production of IL-8, however SNPs of specific interleukins (IL-1B, IL-17) do not qualify as risk factors in the susceptibility of T1DM and CP. More clinical trials are needed on this topic in order to clarify the pathogenetic mechanisms of SNPs in the T1DM genesis in patients with and without CP.

T1DM still needs to be thoroughly explored regarding the ILs polymorphisms panel, however the last 5 years have pointed out some autonomous inflammatory effects which requires further investigations. CP and T1DM association in children and adolescents represents a severe gap in literature that should be filled, the scarce presence of studies also about adults serves as a motivation for ulterior clinical researches.

Author Contributions: Conceptualization, S.D.; methodology, S.D..; validation, S.D., G.V., F.I., M.D., investigation, S.D. and G.V.; resources, G.V.; data curation, G.V.; writing—original draft preparation, S.D., M.D., G.V.; writing—review and editing, S.D. and G.V..; supervision, M.D. and S.D.; project administration, S.D. and F.I. . All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

Appendix A

Table A1. Newcastle-Ottawa Quality Assessment Scale. Possible total points were 4 points for selection, 2 points for comparability and 3 points for exposure [33].

Authors/Year	Selection	Comparability	Exposure	Total Score
Hoffman M. et al. 2022 [13]	3	1	2	6
Li J. et al. 2022 [14]	3	1	2	6
Osman A. E. et al. 2022 [15]	2	1	2	5
Ali Y. et al. 2021 [16]	2	1	2	5
El Helaly R.M. et al. 2021 [17]	3	1	2	6
Haghnazari L. et al. 2021 [18]	3	2	2	7
Hehenkamp P. et al. 2021 [19]	2	1	2	5
Kumar S. et al. 2021 [20]	3	1	2	6
Li J. et al. 2021 [21]	3	2	2	7
Osman A. E. et al. 2021 [22]	2	1	2	5
Tangjittipokin W. et al. 2021 [23]	3	1	2	6
Campos L. P. et al. 2020 [24]	3	1	2	6
Keindl M. et al. 2020 [25]	3	2	1	6
Sharma C. et al. 2020 [26]	2	2	2	6

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Boechat-Fernandes A. et al. 2019 [27]	1	1	1	3
Borilova Linhartova P. et al. 2019 [28]	3	1	2	6
Campos L. P. et al. 2019 [29]	3	1	2	6
Lundtoft C. et al. 2019 [30]	3	2	2	7
Borilova Linhartova P. et al. 2018 [9]	3	2	2	7
Seyfarth J. et al. 2018 [31]	3	1	2	6
Al-Lahham Y. et al. 2017 [32]	3	1	2	6

Table A2. Articles matching inclusion criteria. CP, chronic periodontitis.

Authors/Year	Conclusions
Hoffman M. et al. 2022 [13]	There is higher sIL-7R serum concentrations at T1DM onset and decreasing levels during therapy, whereas IL-7 was only higher in long term patients as compared to controls.
Li J. et al. 2022 [14]	Increased serum IL-17A is a risk factor for autoimmune T1D.
Osman A. E. et al. 2022 [15]	The SNP associated with low production of IL-4 increases the risk of T1DM in young individuals carrying vulnerable HLA alleles/haplotypes.
Ali Y. et al. 2021 [16]	IL-18 gene promoter polymorphisms might be associated with susceptibility to T1D in Egyptian children.
El Helaly R.M. et al. 2021 [17]	AA genotype and A allele of IL-10 rs1518111 SNP could be linked to increased risk for T1DM and DN among Egyptian children.
Haghnazari L. et al. 2021 [18]	The G allele of SNP rs1042522 encoding the TP53 gene for IL-6 increases the risk of developing DM in Iranian population.
Hehenkamp P. et al. 2021 [19]	T1DM monocytes have impaired IL-7 response and lower IL-7R expression.
*Kumar S. et al. 2021 [20]	IL-17A polymorphism was not associated with increased risk for CP in T1DM patients.
Li J. et al. 2021 [21]	The concentration of IL-1β in T1DM patients was significantly higher than that in healthy controls.
Osman A. E. et al. 2021 [22]	ILs levels in T1DM were higher than controls.
Tangjittipokin W. et al. 2021 [23]	IL1B SNPs are associated with T1DM susceptibility.
Campos L. P. et al. 2020 [24]	IL-18 polymorphisms were not associated with T1DM onset in children or adults in this population.
Keindl M. et al. 2020 [25]	IL2RA gene variants might increase the risk of developing vascular complications in people with T1D.
Sharma C. et al. 2020 [26]	IL2-RA gene variants could confer risk alleles for T1D among the Emirati population.
Boechat-Fernandes A. et al. 2019 [27]	SNP in IL18 gene could be associated with DM1 age onset.
*Borilova Linhartova P. et al. 2019 [28]	Variability in the IL-1B and IL-1RN genes may be one of the factors in the susceptibility to T1DM and CP, although the single variants of these polymorphisms are not crucial for the protein production.
Campos L. P. et al. 2019 [29]	IL-6 rs1800795 was not associated with adult-onset T1D. IL-6R rs2228145 was associated with T1D development in adulthood, and carriers of the minor C allele are at increased risk for adult-onset T1D.
Lundtoft C. et al. 2019 [30]	IL-7Rα variants may contribute to disease susceptibility against T1D.
*Borilova Linhartova P. et al. 2018 [9]	CP does not influence the circulating IL-8 levels. Patients with T1DM+CP had higher circulating IL-8

	levels than healthy controls+CP/non-periodontitis.
Seyfarth J. et al. 2018 [31]	Only T1D children with the protective haplotype had lower IL-7 serum levels.
Al-Lahham Y. et al. 2017 [32]	IL-18 rs187238 was not associated with T1D in Euro-Brazilian population.

* Articles considering periodontitis.

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