Value of Serum Sirtuin-1 (SIRT1) Levels and SIRT1 Gene Variants in Periodontitis Patients

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Abstract: Background and Objectives: Periodontitis is a multifactorial inflammatory disease associated with biofilm dysbiosis and is defined by progressive periodontium destruction. Genes largely regulate this entire process. SIRTs are a group of histone deacetylases (HDACs) intimately involved in cell metabolism and are responsible for altering and regulating numerous cell functions. Understanding SIRTs and their functions in periodontitis may be useful for therapeutic treatment strategies in the future. The aim of our study was to investigate the associations amid SIRT1 single-gene nucleotide polymorphisms (rs3818292, rs3758391, and rs7895833) and SIRT1 serum levels for patients affected by periodontitis in the Caucasian population.

Materials and Methods: The study included 201 patients affected by periodontitis and 500 healthy controls. DNA extraction from peripheral leukocytes was carried out using commercial kits. The real-time PCR method was selected for the determination of the genotype of the periodontitis patients and the control group. The ELISA method was used to measure the SIRT1 concentration. A statistical data analysis was performed using “BM SPSS Statistics 27.0” software. Results: The SIRT1 rs3818292 AG genotype was associated with a 2-fold and 1.9-fold increase in the development of periodontitis under the codominant and overdominant models (OR = 1.959; CI = 1.239–3.098; p = 0.004; and OR = 1.944; CI = 1.230–3.073; p = 0.004, respectively). The serum SIRT1 levels were not statistically significantly different between subjects in the periodontitis and control groups (0.984 (5.159) ng/mL vs. 0.514 (7.705) ng/mL, p = 0.792).

Conclusions: in our study, the genotypes and alleles of SIRT1 rs3758391, rs3818292, and rs7895833 statistically significantly differed between the periodontitis and control groups, exclusively in the male population and subjects older than 60 years.

Keywords: periodontitis; SIRT1; rs3758391; rs3818292; rs7895833; SIRT1 levels

1. Introduction

Periodontitis is a complex inflammatory disease, which is interconnected with a dysbiotic biofilm and is characterized by progressive destruction of the periodontium [1]. It is approximated that 538 million people globally are affected by a severe form of periodontitis [2]. Periodontal disease etiology is multifactorial. The host inflammatory and immune response is triggered by the subgingival dental biofilm. This eventually leads to permanent destruction of the periodontium (i.e., alveolar bone and periodontal ligament) in a susceptible host [3].

In the patient’s mouth, the microbiota, immune system, and lifestyle habits interact with each other. This can lead to multiple changes, and the physiology must adapt to keep the host healthy. This whole interplay is regulated mainly by genes [4]. SIRTs are a group...
of histone deacetylases (HDACs), which are divided into seven different members (from SIRT1 to SIRT7) [5]. These proteins are expressed in normal tissues and have an impact on numerous biological processes [6]. Sirtuins, a group of nicotinic adenine dinucleotide (NAD+)-dependent enzymes, are closely related to the metabolism of the cell and are responsible for altering and regulating numerous cellular functions, such as DNA repair, inflammatory responses, apoptosis, aging, or cell cycle [7,8]. Although they belong to the same family, the location of each gene is different. The nucleus locates SIRTs 1, 6, and 7, while SIRT2 is found in the cytosol, and the remaining SIRTs 3, 4, and 5 are detected in the mitochondria [9]. One of the most studied members of the family is SIRT1, which enacts in metabolic health by deacetylation of numerous target proteins in different tissues (heart, muscle, endothelium, liver etc.) and is well known to affect cancer by its suppression or promotion, depending on the cell type or its content [10]. It is also a gene found in all living organisms and is known as the longevity gene [11]. While focusing on various oral diseases and pathologies, the role of some members of the sirtuin gene family remains unclear to date, such as SIRT2, whose part in oral cancer pathogenesis has not yet been looked into. Recently, a correlation between oral malignancies and the SIRT1, SIRT3, and SIRT7 genes and their expressions has been reported [9]. In periodontal diseases, although not directly, some sirtuins (SIRT4- and SIRT3-families) are studied, and there tend to be associations with various pathologies, such as diabetes melitus [12]. Some members of the SIRT family, especially SIRT6, tend to have a therapeutic effect on periapical lesions and their treatment by suppressing CCL2 synthesis, which is also associated with regulatory activities in cellular metabolism [13].

Therefore, understanding SIRT and its functions in oral diseases, such as periodontitis, may be useful for therapeutic strategies in the future [14,15]. SIRT1 had a beneficial effect in reducing vascular senescence in the endothelial cell culture model [16]. An increase in levels of SIRT1 is shown to prevent the progression of periodontal disease in an animal study [17]. Additionally, Caribe et al. have reported that SIRT1 levels tend to increase after periodontal treatment [18,19]. However, a limited number of studies show the association between elevated serum SIRT1 and periodontitis. Therefore, understanding SIRT and its functions in oral diseases, such as periodontitis, may be useful for therapeutic treatment strategies in the future.

The aim of our study was to examine the links connecting SIRT1 single-gene nucleotide polymorphisms (rs3818292, rs3758391, and rs7895833) and SIRT1 serum levels in patients with periodontitis in the Caucasian population.

2. Materials and Methods

The case–control study was conducted at the Department of Prosthodontics, Lithuanian University of Health Sciences Hospital, and the Neuroscience Institute of the Lithuanian University of Health Sciences.

2.1. Ethics Statement

The Lithuanian University of Health Sciences Ethics Committee has approved the study for Biomedical Research (No. BE-2-20). All subjects gave written informed consent in accordance with the Declaration of Helsinki.

2.2. Control and Patients with Periodontitis Group Formation

The study consisted of 201 patients with periodontitis (n = 201) and 500 healthy control subjects (n = 500).

All the patients selected for the study met the following criteria: (i) over 18 years of age, (ii) had more than 30% of their mouth affected by periodontitis, leading to a diagnosis of generalized periodontal disease, (iii) consented to intraoral and radiographic examination to determine the extent of periodontitis.

Patients were excluded from the study if they met any of the following statements: (i) had undergone chemotherapy, (ii) tooth loss was not due to periodontal disease but to
other causes (patients’ previous dental records indicating trauma and tooth extractions due to treatment of jaw fractures), (iii) no radiological examination with orthopantomogram was performed, (iv) the mouth was completely edentulous, (v) systemic diseases, e.g., diabetes mellitus, malignant tumors, systemic connective tissue diseases, (vi) chronic infectious/non-infectious diseases or conditions after organ or tissue transplantation, (vii) diseases of the cardiovascular system; (viii) regular smokers and alcohol abusers.

2.3. Odontological Examination

The study participants underwent intraoral and radiographic examinations at their first visit to the prosthodontist. Periodontal disease was diagnosed according to the consensus report of Working Group 2 of the World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions 2017 [20]. The study included patients with all three different stages of periodontitis (I, II, and III). The extent of periodontitis was >30% of the total affected teeth in the subject’s mouth, in all the patients. The periodontitis-affected patients underwent radiographic examination to determine if bone loss was present and to evaluate it (orthopantomogram, dental radiographs and proximal digital radiographs were examined).

2.4. DNA Extraction, Genotyping, and Enzyme-Linked Immunosorbent Assay

DNA samples were extracted from peripheral venous blood using the DNA salting-out method. Genotyping of all three SNPs was performed using TaqMan® genotyping assays (Applied Biosystems, Foster City, CA, USA) and SIRT1 (rs3818292, rs3758391, and rs7895833) according to the manufacturer’s instructions using real-time polymerase chain reaction (PCR). Serum SIRT1 levels were determined in 500 control subjects and 201 patients with periodontitis. Serum SIRT1 levels in patients were determined using the commercial enzyme-linked immunosorbent assay (ELISA) kit for human SIRT1 (Human SIRT1 ELISA Kit, Abcam, Cambridge, United Kingdom) according to the manufacturer’s instructions, and optical density was measured immediately at a wavelength of 450 nm, using a microplate reader (Multiskan FC microplate photometer, Thermo Scientific, Waltham, MA, USA). The SIRT1 level was calculated using the standard curve; sensitivity range of the standard curve was 0.63–40 ng/mL, sensitivity 132 pg/mL [21].

2.5. Statistical Analysis

SPSS/W 27.0 software (Statistical Package for the Social Sciences for Windows, Inc., Chicago, IL, USA) was used for the statistical analysis. Absolute numbers with percentages were used for data expression. Percentages were used for genotype frequencies expressions. A Hardy–Weinberg analysis was performed to compare the observed and expected frequencies of SIRT1 (rs3818292, rs3758391, and rs7895833) with the χ² test in all the groups. The χ² test was used for the distribution comparison of SIRT1 (rs3818292, rs3758391, and rs7895833) in the periodontitis and control groups. The estimation of the influence of genotypes on the development of periodontitis was performed by the binomial logistic regression analysis. Odds ratios and 95% confidence intervals were presented. The best genetic model selection was based on the Akaike Information Criterion (AIC); consequently, the lowest AIC values represented the best genetic models.

3. Results

There was no deviation of the genotypes of the tested SNPs from the Hardy–Weinberg equilibrium (HWE) (p > 0.05). The study group included 201 patients with periodontitis; 85 (42.73%) were men and 116 (57.7%) were women. The median age was 70.0 years (IQR = 16). The control group consisted of 500 subjects; 250 were men and 250 women; the median age was 66.00 years (IQR = 15). The age and gender did not statistically significantly differ between the groups (p = 0.082, p = 0.065, respectively) (Table 1).
Table 1. Demographic characteristics of the study population.

| Characteristic | Group | Periodontitis | Control Group | p-Value |
|----------------|-------|---------------|---------------|---------|
|                |       | n = 201       | n = 500       |         |
| Males, n (%)   |       | 85 (42.73%)   | 250 (50%)     | 0.065   |
| Females, n (%) |       | 116 (57.7%)   | 250 (50%)     |         |
| Age, median (IQR) |   | 70.0 (16)     | 66.00 (15)    | 0.082   |

p-value—significance level.

The genotypes and allele distributions of SIRT1 rs3818292 and rs7895833 were statistically significantly different between the periodontitis and the control group. The analysis showed that the SIRT1 rs3818292 AA genotype was less frequent in the periodontitis group than in the control group (80.6% vs. 89.2%, p = 0.002), while the AG genotype was more frequent in the periodontitis group than in the control group (18.4% vs. 10.4%, p = 0.004). The G allele was more frequent in the periodontitis group than in the control group (10.2% vs. 5.4%, p = 0.001). The SIRT1 rs7895833 AA genotype was less frequent in the periodontitis group than in the control group (66.2% vs. 76.6%, p = 0.005), while AG was more frequent in the periodontitis group than in the control group (32.3% vs. 22.2% p = 0.005). The G allele was more frequent in the periodontitis group than in the control group (17.7% vs. 12.3%, p = 0.009) (Table 2).

Table 2. Genotype and allele distribution of SIRT1 rs3818292, rs3758391, and rs7895833 in periodontitis and control groups.

| Genotype/Allele | Periodontitis | Control Group | HWE p-Value | p-Value |
|-----------------|---------------|---------------|-------------|---------|
|                  | n = 201       | n = 500       |             |         |
| rs3818292       |               |               |             |         |
| AA              | 162 (80.6)    | 446 (89.2)    | 0.715       | 0.009   |
| AG              | 37 (18.4)     | 52 (10.4)     |             |         |
| GG              | 2 (1.0)       | 2 (0.4)       |             |         |
| Total           | 201 (100.0)   | 500 (100.0)   |             |         |
| A               | 361 (89.8)    | 976 (94.6)    |             |         |
| G               | 41 (10.2)     | 56 (5.4)      |             |         |
| Rs3758391       |               |               |             |         |
| CC              | 103 (51.2)    | 288 (57.6)    | 0.179       | 0.272   |
| CT              | 86 (42.8)     | 190 (38.0)    |             |         |
| TT              | 12 (6.0)      | 22 (4.4)      |             |         |
| Total           | 201 (100.0)   | 500 (100.0)   |             |         |
| A               | 292 (72.6)    | 766 (76.6)    |             | 0.119   |
| T               | 110 (27.4)    | 234 (23.4)    |             |         |
| rs7895833       |               |               |             |         |
| AA              | 133 (66.2)    | 383 (76.6)    | 0.517       | 0.018   |
| AG              | 65 (32.3)     | 111 (22.2)    |             |         |
| GG              | 3 (1.5)       | 6 (1.2)       |             |         |
| Total           | 201 (100.0)   | 500 (100.0)   |             |         |
| A               | 331 (82.3)    | 877 (87.7)    |             |         |
| G               | 71 (17.7)     | 123 (12.3)    |             | 0.009   |

p-value—significance level; 1 (AA vs. AG + GG) p = 0.002; 2 (AG vs. AA + GG) p = 0.004; 3 (AA vs. AG + GG) p = 0.005; 4 (AG vs. AA + GG) p = 0.005.

Further binary logistic regression analysis was conducted to evaluate the effects of these SNPs on periodontitis in males. The analysis revealed that the SIRT1 rs3818292 AG genotype was associated with 2-fold and 1.9-fold increased odds of periodontitis development under the codominant and overdominant models (OR = 1.959; CI = 1.239–3.098; p = 0.004; and OR = 1.944; CI = 1.230–3.073; p = 0.004, respectively). The AG + GG geno-
types were also associated with 2-fold increased odds of periodontitis development under the dominant model (OR = 1.988; CI = 1.269–3.116; \( p = 0.003 \)). Each G allele increased the odds of periodontitis development by 1.9-fold in the additive model (OR = 1.905; CI = 1.249–2.906; \( p = 0.003 \)).

The \( SIRT1 \) rs7895833 AG genotype was associated with 1.7-fold increased odds of periodontitis development under the codominant and overdominant models (OR = 1.686; CI = 1.172–2.427; \( p = 0.005 \); and OR = 1.675; CI = 1.165–2.408; \( p = 0.005 \), respectively). The AG + GG genotypes were associated with 1.7-fold increased odds of periodontitis development under the dominant model (OR = 1.674; CI = 1.170–2.394; \( p = 0.005 \)). Each G allele increased the odds of periodontitis development by 1.6-fold in the additive model (OR = 1.572; CI = 1.129–2.188; \( p = 0.007 \)) (Table 3).

Table 3. Binomial logistic regression analysis of periodontitis and control groups.

| Model | Genotype/Allele | OR (95% CI) | \( p \)-Value | AIC  |
|-------|-----------------|-------------|---------------|-----|
| **Periodontitis** | | | | |
| **SIRT1 rs3818292** | | | | |
| Co-dominant | AG vs. AA | 1.959 (1.239–3.098) | 0.004 | 835.292 |
| | GG vs. AA | 2.753 (0.385–19.706) | 0.313 | |
| Dominant | AG + GG vs. AA | 1.988 (1.269–3.116) | 0.003 | 833.402 |
| Recessive | GG vs. AG + AA | 2.503 (0.350–17.888) | 0.361 | 841.271 |
| Overdominant | AG vs. AA + GG | 1.944 (1.230–3.073) | 0.004 | 834.284 |
| Additive | G | 1.905 (1.249–2.906) | 0.003 | 833.384 |
| **SIRT1 rs3758391** | | | | |
| Co-dominant | CT vs. CC | 1.266 (0.901–1.778) | 0.174 | 841.503 |
| | TT vs. CC | 1.525 (0.729–3.192) | 0.263 | |
| Dominant | CT + TT vs. CC | 1.293 (0.931–1.795) | 0.126 | 839.739 |
| Recessive | TT vs. CT + CC | 1.380 (0.669–2.843) | 0.383 | 841.343 |
| Overdominant | CT vs. CC + TT | 1.220 (0.875–1.702) | 0.241 | 840.711 |
| Additive | T | 1.252 (0.952–1.646) | 0.108 | 839.515 |
| **SIRT1 rs7895833** | | | | |
| Co-dominant | AG vs. AA | 1.686 (1.172–2.427) | 0.005 | 836.236 |
| | GG vs. AA | 1.440 (0.385–5.383) | 0.610 | |
| Dominant | AG + GG vs. AA | 1.674 (1.170–2.394) | 0.005 | 834.284 |
| Recessive | GG vs. AG + AA | 1.247 (0.309–5.037) | 0.756 | 841.985 |
| Overdominant | AG vs. AA + GG | 1.675 (1.165–2.408) | 0.005 | 834.486 |
| Additive | G | 1.572 (1.129–2.188) | 0.007 | 835.030 |

OR—odds ratio; CI—confidence interval; \( p \)-value—significance level; AIC—Akaike information criteria.

The genotype and allele distributions of \( SIRT1 \) rs3818292 and rs7895833 were statistically significantly different between the periodontitis and control groups when distinguished between gender. The analysis revealed that the \( SIRT1 \) rs3818292 AA genotype was less frequent in the male periodontitis group than in the control group (77.6% vs. 88.8%, \( p = 0.010 \)), while the AG genotype was more frequent in the periodontitis group than in the control group (22.4% vs. 10.8%, \( p = 0.008 \)). The G allele was more frequent in the male periodontitis group than in the control group (11.2% vs. 5.8%, \( p = 0.019 \)). In addition, the \( SIRT1 \) rs7895833 AA genotype was less frequent in the periodontitis group than in the control group (60.0% vs. 75.2%, \( p = 0.007 \)), while the AG genotype was more frequent in the periodontitis group than in the control group (37.6% vs. 23.6% \( p = 0.012 \)). The G allele was more frequent in the periodontitis group than in the control group (21.2% vs. 13.0%, \( p = 0.010 \)) (Table 4). In addition, the analysis revealed that the \( SIRT1 \) rs3818292 G allele was more frequent in the female periodontitis group than in the control group (9.5% vs. 5.4%, \( p = 0.001 \)) (Table 5).
Table 4. Genotype and allele distribution of SIRT1 rs3818292, rs3758391, and rs7895833 in periodontitis and control groups between males.

| Genotype/Allele | Periodontitis $n = 85$ $n$ (%) | Control Group $n = 250$ $n$ (%) | $p$-Value |
|-----------------|---------------------------------|---------------------------------|-----------|
| **Males**       |                                 |                                 |           |
| rs3818292       |                                 |                                 |           |
| AA              | 66 (77.6)                       | 222 (88.8)                      | 0.024     |
| AG              | 19 (22.4)                       | 27 (10.8)                       |           |
| GG              | 0 (0)                           | 1 (0.4)                         |           |
| Total           | 85 (100.0)                      | 250 (100.0)                     |           |
| A               | 151 (88.8)                      | 471 (94.2)                      |           |
| G               | 19 (11.2)                       | 29 (5.8)                        |           |
| rs3758391       |                                 |                                 |           |
| CC              | 43 (50.6)                       | 144 (57.6)                      | 0.631     |
| CT              | 36 (42.4)                       | 96 (38.4)                       |           |
| TT              | 6 (7.1)                         | 10 (4.0)                        |           |
| Total           | 85 (100.0)                      | 250 (100.0)                     |           |
| C               | 122 (71.8)                      | 364 (76.8)                      | 0.187     |
| T               | 48 (28.2)                       | 116 (23.2)                      |           |
| rs7895833       |                                 |                                 |           |
| AA              | 51 (60.0)                       | 188 (75.2)                      | 0.027     |
| AG              | 32 (37.6)                       | 59 (23.6)                       |           |
| GG              | 2 (2.4)                         | 3 (1.2)                         |           |
| Total           | 85 (100.0)                      | 250 (100.0)                     |           |
| A               | 134 (78.8)                      | 435 (87.0)                      | 0.010     |
| G               | 46 (21.2)                       | 65 (13.0)                       |           |

$p$-value—significance level; $^1$ (AA vs. AG + GG) $p = 0.010$; $^2$ (AG vs. AA + GG) $p = 0.008$; $^3$ (AA vs. AG + GG) $p = 0.007$; $^4$ (AG vs. AA + GG) $p = 0.012$.

Table 5. Genotype and allele distribution of SIRT1 rs3818292, rs3758391, and rs7895833 in periodontitis and control groups between females.

| Genotype/Allele | Periodontitis $n = 116$ $n$ (%) | Control Group $n = 250$ $n$ (%) | $p$-Value |
|-----------------|---------------------------------|---------------------------------|-----------|
| **Females**     |                                 |                                 |           |
| rs3818292       |                                 |                                 |           |
| AA              | 96 (82.8)                       | 224 (89.6)                      | 0.124     |
| AG              | 18 (15.5)                       | 25 (10.0)                       |           |
| GG              | 2 (1.7)                         | 1 (0.4)                         |           |
| Total           | 116 (100.0)                     | 250 (100.0)                     |           |
| A               | 210 (90.5)                      | 473 (94.6)                      | 0.039     |
| G               | 22 (9.5)                        | 27 (5.4)                        |           |
| rs3758391       |                                 |                                 |           |
| CC              | 60 (51.7)                       | 144 (57.6)                      | 0.570     |
| CT              | 50 (43.1)                       | 94 (37.6)                       |           |
| TT              | 6 (5.2)                         | 12 (4.8)                        |           |
| Total           | 116 (100.0)                     | 250 (100.0)                     |           |
| C               | 170 (73.3)                      | 362 (76.4)                      | 0.361     |
| T               | 62 (26.7)                       | 118 (23.6)                      |           |
| rs7895833       |                                 |                                 |           |
| AA              | 82 (70.7)                       | 195 (78.0)                      | 0.267     |
| AG              | 33 (28.4)                       | 52 (20.8)                       |           |
| GG              | 1 (0.9)                         | 3 (1.2)                         |           |
| Total           | 116 (100.0)                     | 250 (100.0)                     |           |
| A               | 197 (84.9)                      | 442 (88.4)                      | 0.188     |
| G               | 35 (15.1)                       | 58 (11.6)                       |           |

$p$-value—significance level.
In addition, we performed a binary logistic regression analysis to evaluate the effects of these SNPs on periodontitis in males. The analysis revealed that the SIRT1 rs3818292 AG genotype was associated with 2.4-fold increased odds of periodontitis development under the codominant and overdominant models (OR = 2.367; CI = 1.238–4.525; \( p = 0.009 \) and OR = 2.378; CI = 1.244–4.545; \( p = 0.009 \), respectively). In addition, the AG + GG genotypes were associated with 2.3-fold increased odds of periodontitis development under the dominant model (OR = 2.282; CI = 1.199–4.347; \( p = 0.012 \)). Each G allele increased the odds of periodontitis development by 2.1-fold in the additive model (OR = 2.110; CI = 1.129–3.945; \( p = 0.019 \)). The SIRT1 rs7895833 AG genotype was associated with 2-fold increased odds of periodontitis under the codominant and overdominant models (OR = 1.999; CI = 1.177–3.397; \( p = 0.01 \) and OR = 1.955; CI = 1.154–3.311; \( p = 0.013 \)), respectively. Each G allele increased the odds of periodontitis development by 1.9-fold in the additive model (OR = 1.888; CI = 1.173–3.038; \( p = 0.009 \)) (Table 6). Therefore, no statistically significant associations were found in the women’s periodontitis and control groups (data not shown).

Table 6. Genotype and allele distribution of SIRT1 rs3818292, rs3758391, and rs7895833 in periodontitis and control groups within males.

| Model       | Genotype/Allele | OR (95% CI)         | \( p \)-Value | AIC    |
|-------------|-----------------|---------------------|--------------|--------|
| **Males**   |                 |                     |              |        |
| **SIRT1 rs3818292** |                 |                     |              |        |
| Co-dominant | AG vs. AA       | 2.367 (1.238–4.525) | 0.009        | 376.41 |
|             | GG vs. AA       | -                   | -            | -      |
| Dominant    | AG + GG vs. AA  | 2.282 (1.199–4.347) | 0.012        | 374.56 |
| Recessive   | GG vs. AG + AA  | -                   | -            | -      |
| Overdominant| AG vs. AA + GG  | 2.378 (1.244–4.545) | 0.009        | 377.93 |
| Additive    | G               | 2.110 (1.129–3.945) | 0.019        | 376.24 |
| **SIRT1 rs3758391** |                 |                     |              |        |
| Co-dominant | CT vs. CC       | 1.256 (0.752–2.097) | 0.384        | 381.53 |
|             | TT vs. CC       | 2.009 (0.691–5.846) | 0.200        | 380.23 |
| Dominant    | CT + TT vs. CC  | 1.327 (0.810–2.174) | 0.261        | 380.28 |
| Recessive   | TT vs. CT + CC  | 1.823 (0.642–5.175) | 0.259        | 380.28 |
| Overdominant| CT vs. CC + TT  | 1.179 (0.715–1.943) | 0.520        | 380.28 |
| Additive    | T               | 1.329 (0.882–2.002) | 0.174        | 379.66 |
| **SIRT1 rs7895833** |                 |                     |              |        |
| Co-dominant | AG vs. AA       | 1.999 (1.177–3.397) | 0.010        | 376.55 |
|             | GG vs. AA       | 2.458 (0.400–15.103)| 0.332        | 374.60 |
| Dominant    | AG + GG vs. AA  | 2.022 (1.201–3.401) | 0.008        | 374.60 |
| Recessive   | GG vs. AG + AA  | 1.984 (0.326–12.079)| 0.457        | 374.78 |
| Overdominant| AG vs. AA + GG  | 1.955 (1.154–3.311) | 0.013        | 375.42 |
| Additive    | G               | 1.888 (1.173–3.038) | 0.009        | 374.78 |

OR—odds ratio; CI—confidence interval; \( p \)-value—significance level; AIC—Akaike information criteria.

The genotypes and allele distributions of SIRT1 rs3818292 and rs7895833 were statistically significantly different between the periodontitis group and the control group of patients older than 60 years. The analysis showed that the SIRT1 rs3818292 AA genotype was less frequent in the periodontitis group than in the control group (78.1% vs. 89.4%, \( p = 0.001 \)), while the AG genotype was more frequent in patients over 60 years old than in the control group (20.5% vs. 10.6%, \( p = 0.003 \)). The G allele was more frequent in the periodontitis group than in the control group (11.6% vs. 5.2%, \( p = 0.001 \)). The genotype of SIRT1 rs7895833 AA was less frequent in the periodontitis group than in the control group (64.2% vs. 76.1%, \( p = 0.006 \)), while the genotype AG was more frequent in the periodontitis group than in the control group (33.8% vs. 22.8% \( p = 0.001 \)). The G allele was more frequent
in the periodontitis group than in the control group (18.9% vs. 12.5%, \( p = 0.008 \)) (Table 7). No statistically significant associations were found between the periodontitis and control groups within the 60-year-old or younger population (data not shown).

Table 7. Genotype and allele distribution of \( SIRT1 \) rs3818292, rs3758391, and rs7895833 in periodontitis and control groups between patients older than 60 years old.

| Genotype/Allele | Periodontitis \( n = 151 \) | Control Group \( n = 368 \) | \( p \)-Value |
|-----------------|-----------------------------|-----------------------------|--------------|
| rs3818292       |                             |                             |              |
| AA              | 118 (78.1) \(^1\)           | 329 (89.4) \(^1\)           | 0.001        |
| AG              | 31 (20.5) \(^2\)            | 39 (10.6) \(^2\)            |              |
| GG              | 2 (1.3)                     | 0 (0)                       |              |
| Total           | 151 (100.0)                 | 368 (100.0)                 |              |
| A               | 267 (88.4)                  | 697 (94.7)                  | 0.001        |
| G               | 35 (11.6)                   | 39 (5.2)                    |              |
| rs3758391       |                             |                             |              |
| CC              | 74 (49.0)                   | 209 (56.8)                  | 0.187        |
| CT              | 67 (44.4)                   | 144 (39.1)                  |              |
| TT              | 10 (6.6)                    | 15 (4.1)                    |              |
| Total           | 151 (100.0)                 | 368 (100.0)                 |              |
| C               | 215 (71.2)                  | 562 (76.4)                  | 0.081        |
| T               | 87 (28.8)                   | 174 (23.6)                  |              |
| rs7895833       |                             |                             |              |
| AA              | 97 (64.2) \(^3\)           | 280 (76.1) \(^3\)           | 0.022        |
| AG              | 51 (33.8) \(^4\)           | 84 (22.8) \(^4\)           |              |
| GG              | 3 (2.0)                     | 4 (1.1)                     |              |
| Total           | 151 (100.0)                 | 368 (100.0)                 |              |
| A               | 245 (81.1)                  | 644 (87.5)                  |              |
| G               | 57 (18.9)                   | 92 (12.5)                   |              |

\( p \)-value—significance level; \(^1\) (AA vs. AG + GG) \( p = 0.001 \); \(^2\) (AG vs. AA + GG) \( p = 0.003 \); \(^3\) (AA vs. AG + GG) \( p = 0.006 \); \(^4\) (AG vs. AA + GG) \( p = 0.001 \). Moreover, a binary logistic regression analysis was also performed in the group of patients older than 60 years to evaluate the impact of these SNPs on periodontitis. The analysis revealed that the \( SIRT1 \) rs3818292 AG genotype was associated with 2.2-fold increased odds of periodontitis development under the codominant and overdominant models in the over-60-year-old group (OR = 2.216; CI = 1.322–3.714; \( p = 0.003 \); and OR = 2.179; CI = 1.301–3.925; \( p = 0.001 \), respectively). In addition, the AG + GG genotypes were associated with 2.4-fold increased odds of periodontitis development according to the dominant model (OR = 2.359; CI = 1.418–3.925; \( p = 0.001 \)). Each G allele increased the odds of periodontitis development by 2.4-fold in the additive model (OR = 2.408; CI = 1.474–3.933; \( p = 0.001 \)). The \( SIRT1 \) rs7895833 AG genotype was associated with a 1.8-fold increase in the odds of periodontitis development in the codominant model and a 1.7-fold increase in the overdominant model (OR = 1.753; CI = 1.154–2.661; \( p = 0.008 \); and OR = 1.724; CI = 1.138–2.614; \( p = 0.01 \), respectively). The AG + GG genotypes were also associated with 1.8-fold increased odds of developing periodontitis under the dominant model (OR = 1.771; CI = 1.176–2.669; \( p = 0.006 \)). Each G allele increased the odds of periodontitis development by 1.7-fold in the additive model (OR = 1.688; CI = 1.157–2.463; \( p = 0.007 \)) (Table 8).
Table 8. Binomial logistic regression analysis of periodontitis and control groups in the older than 60-year-old patients’ group.

| Model            | Genotype/Allele                | OR (95% CI)        | p-Value | AIC   |
|------------------|--------------------------------|--------------------|---------|-------|
| **SIRT1 rs3818292** |                                |                    |         |       |
| Co-dominant      | AG vs. AA                       | 2.216 (1.322–3.714) | 0.003   | 616.12|
|                  | GG vs. AA                       | 4.5 × 10⁹ (0.000)  | 1.0     |       |
| Dominant         | AG + GG vs. AA                  | 2.359 (1.418–3.925) | 0.001   | 617.31|
| Recessive        | GG vs. AG + AA                  | 4.0 × 10⁹ (0.000)  | 1.0     |       |
| Overdominant     | AG vs. AA + GG                  | 2.179 (1.301–3.650) | 0.003   | 619.43|
| Additive         | G                               | 2.408 (1.474–3.933) | 0.001   | 615.81|
| **SIRT1 rs3758391** |                                |                    |         |       |
| Co-dominant      | CT vs. CC                       | 1.314 (0.887–1.946) | 0.173   | 626.63|
|                  | TT vs. CC                       | 1.883 (0.810–4.374) | 0.141   |       |
| Dominant         | CT + TT vs. CC                  | 1.368 (0.935–2.000) | 0.106   | 625.30|
| Recessive        | TT vs. CT + CC                  | 1.669 (0.732–3.803) | 0.223   | 626.48|
| Overdominant     | CT vs. CC + TT                  | 1.241 (0.846–1.820) | 0.270   | 626.70|
| Additive         | T                               | 1.340 (0.976–1.840) | 0.070   | 624.65|
| **SIRT1 rs7895833** |                                |                    |         |       |
| Co-dominant      | AG vs. AA                       | 1.753 (1.154–2.661) | 0.008   | 622.50|
|                  | GG vs. AA                       | 2.165 (0.476–9.846) | 0.318   |       |
| Dominant         | AG + GG vs. AA                  | 1.771 (1.176–2.669) | 0.006   | 620.57|
| Recessive        | GG vs. AG + AA                  | 1.845 (0.408–8.342) | 0.427   | 627.30|
| Overdominant     | AG vs. AA + GG                  | 1.724 (1.138–2.614) | 0.010   | 621.44|
| Additive         | G                               | 1.688 (1.137–2.463) | 0.007   | 620.67|

OR—odds ratio; CI—confidence interval; p-value—significance level; AIC—Akaike information criteria.

Figure 1 shows the SIRT1 serum levels in periodontitis patients and control group subjects. An evaluation of serum SIRT1 levels was performed in seven periodontitis-affected patients and five control group subjects. We found that SIRT1 serum levels were not statistically significantly different between the periodontitis patients and control group subjects (0.984 (5159) ng/mL vs. 0.514 (7705) ng/mL, p = 0.792) (Figure 1).
4. Discussion

Several factors and mechanisms must be considered when studying the relationship between periodontitis and sirtuin activity. In research carried out by Caribe et al., SIRT1 was linked with protection against inflammation when two groups of patients (forty periodontal patients and thirty-eight healthy individuals) were compared before and after periodontal treatment; SIRT1 levels tend to increase after periodontal treatment [18]. In another study, researchers Kude et al. investigated periapical periodontitis. The results showed that SIRT1 might affect angiogenesis in periapical granulomas, and the mechanism was based on the activation of endothelial cell proliferation, along with VE-cadherin and VEGF expression [22]. It is important to note that in mammalian cells, SIRT1 works as a regulator for the release suppression of inflammatory mediators. A study by Qu et al. showed that the activation of SIRT1 significantly impaired and suppressed the expression of MMP-13 by focusing on NF-κB p65 [23]. Periodontitis has also been associated with numerous other diseases, including coronary artery disease. Caribe et al. conducted a study showing that periodontal disease treatment decreased the mannose-binding lectin concentration (a protein of the immune system that tends to bind to pathogens in periodontal disease) and increased the serum SIRT1 concentration in the group of patients who were and were not affected by coronary artery disease [19].

Nevertheless, cell regeneration is another important aspect of analyzing periodontal treatment options. The research results of Lee et al. covered SIRT1 activation by resveratrol in various cells; periodontal ligament cells, cementum, and osteoblasts showed an increased mineralized nodules formation and the over-expression of mRNAs [24]. It should also be noted that the overexpression of SIRT1 promotes periodontal ligament cell differentiation into osteoblast-like cells and affects the said cells’ mineralization, while periodontal cell differentiation is blocked by the suppression of SIRT1 [24]. In a study by Zhang et al., rs3758391/CC was found to be more prevalent in comparison to rs3758391/CT and rs3758391/TT in subjects who were older than 60 years (odds ratio = 3.042, p = 0.027) [25], although in our research, there were no statistically significant results related to periodontal inflammation for the same polymorphism and age group. Furthermore, Yue et al. investigated the associations between SIRT1 gene polymorphisms and diabetic kidney disease, where rs3818292 patients with the GG genotype in the rs3818292 locus were 0.23-fold and 0.21-fold higher than for AA and for AA + AG genotypes, respectively, which in our case, the AG + GG genotypes were associated with 2-fold increased odds of periodontitis development in the dominant model (OR = 1.988; CI = 1.269–3.116; p = 0.003). In the work of Hou et al., the AA genotype of rs7895833 was associated with a significantly decreased risk of CRS1 (OR = 0.49), whereas in our study, the genotype AA was less frequent in the periodontitis patients’ group, in comparison to the control group (60.0% vs. 75.2%, p = 0.007) in the male population. The following study also proved that the two SIRT1 rs1467568 and rs7895833 polymorphisms had an impact on the reduced risk of developing CRS1 in the Chinese population [26]. In the work of Vaiciulis et al., which focused on the study of laryngeals squamous cell carcinoma (LSCC) development probability, carriers of the SIRT1 rs3758391 T/T genotype had a statistically significant increased probability of developing advanced-stage LSCC, according to the codominant and recessive genetic model (OR = 2.387; 95% CI = 1.091–5.222; p = 0.029 and OR = 2.287; 95% CI = 1.070–4.888; p = 0.033, respectively) [27]. In contrast, in our study, we found no statistically significant differences in the development of periodontitis in the male population in our study.

The SIRT2 family was also shown to have an impact on periodontal disease cases. Kluknavska et al. concluded that SIRT2 is increased in aggressive and chronic periodontitis, compared to healthy individuals [28]. On the other hand, SIRT3 plays a functional role in age-related periodontal diseases and their underlying mechanisms. As Chen et al. found, a decrease in SIRT3 abundance affects age-related periodontal disease by exacerbating oxidative stress and promoting mitochondrial dysfunction [29]. In addition, SIRT3 and SIRT4 play an important role in analyzing blood glucose levels in patients suffering from diabetes mellitus. This is important for early diagnosis and for people who do not respond...
to other drugs [12]. It is important to note that SIRT3 and its inhibitors are a promising new avenue to explore the development of therapies for other oral diseases, such as head and neck cancer, by inhibiting cell proliferation and promoting apoptosis [30]. In the work of Yang et al., which focused on the role of SIRT5 in apical periodontitis, the results showed that SIRT5 expression decreased, oxidative stress increased, and apoptosis was enhanced in bone tissue cells [14]. This led the researchers to conclude that increasing SIRT5 may potentially be a therapeutic treatment for apical periodontitis [14]. As for the activity of SIRT6 in the pathogenesis of periapical lesions, a study by Kok et al. showed that SIRT6 has an effect on the suppression of glycolysis enhanced by hypoxia and can inhibit apoptosis induced by hypoxia or treatment with lactate [31]. This indicates that SIRT6 plays a role as a negative regulator of inflammation. It may also positively alleviate periapical lesions by suppressing osteoblastic glycolysis and apoptosis [31]. Researchers Lee et al. also investigated the ability of SIRT6 to suppress the synthesis of CCL2 (chemokine ligand 2), which may lead to a therapeutic effect on periapical lesions [13]. As noted by Huang et al., SIRT6 also played a negative role in the differentiation and mineralization of cementoblasts, which was important because of the similar composition of cementum and its importance in homeostasis during periodontal treatment [32]. Although no recent data on SIRT7 and periodontal disease could be found at the time of this review, downregulation of SIRT7 is observed in carcinomas. A study by Li et al. showed that SIRT7 is downregulated in OSCC cell lines and human OSCC/OSCC tissues with lymph node metastases, which functions by preventing SMAD4 deacetylation [33]. Further long-term studies are needed to investigate and evaluate the changes and their impact on the above biomarkers, in terms of prognosis and further progression of periodontal disease.

Some limitations of this study must be acknowledged. The sample size was relatively small in our study, and further research with a larger sample is needed.

5. Conclusions

SIRT1 rs3818292 and rs7895833 might be associated with decreased odds of PD development exclusively in the male population, in subjects older than 60 years. Serum SIRT1 levels were not statistically significantly different between subjects in the periodontitis and control groups.

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