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ORIGINAL ARTICLE

Transforming growth factor-β profile in cyclosporine-A induced gingival enlargement in renal transplant patients

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1. Introduction

Gingival enlargement, a common feature of gingival disease, has been described as an increase in the size of the gingiva (Agrawal, 2015). Gingival overgrowth (GO) secondary to prescription drugs was first reported in 1939 by Kimball following the chronic use of an anti-epileptic drug by institutionalised children receiving phenytoin (Dilantin) therapy for the treatment of seizures (Tripathi et al, 2015).

The aetiology of drug-induced GO is not completely understood but is thought to be multifactorial. Today, over 20 pharmacological formulations have been associated with GO. These drugs are classified into three categories: calcium-channel blockers, anticonvulsants and immunosuppressants (Rees and Levine, 1995). The pharmaceutical company Sandoz first introduced the immunosuppressant cyclosporine A (CsA) in 1976; CsA was isolated as an antifungal and registered in 1983 (Borel et al, 1976; Dreyfuss et al., 1976).

Since then, CsA has been regarded as a principal tool to prevent organ transplant rejection. However, CsA has often been associated with several side effects, including GO (Kim et al, 2008). It is estimated that about 30% of patients receiving CsA have induced GO (Mishra et al, 2012).

CsA is erratically absorbed in the gut and reaches peak plasma concentration within 3–4 h. The drug is metabolised in the liver; after almost six hours, CsA is evacuated mostly via the bile and faeces (Venkataramanan et al, 1985). CsA is 95% bound with variable degrees of affinity to the following cells: erythrocytes (50%), lipoproteins (40%) and 5% being found free in the plasma (Rodl and Khoshsorur, 1990). CsA affects patients' daily lives by impairing their physical appearance and masticatory function. Furthermore, these outcomes are often associated with a psychological impact, which also affects patient compliance with CsA treatment regimens (Hassell and Hefti, 1991).

CsA mainly suppresses some T and B lymphocyte subpopulation functions (Kaufmann et al, 1974) (12). As a result of CsA-stimulated gingival overgrowth, a transformation takes place in the cytokine interleukin 6 (IL-6) and also in transforming growth factor-ß1 (TGF-ß1), which play a supervisory role in periodontal tissue turnover (Chae et al., 2006). Furthermore, IL-6 also has a multifunctional regulatory role in some immune responses, haematopoiesis and cell hyperplasia regulation. Choy and Rose-John reported that the increased appearance of cellular IL-6 within the gingival connective tissue stimulates the formation of gingival lesions (Choy and Rose-John, 2017).

Spolidorio et al studied the effects of cyclosporine on gingival diseases in rats. After both 60 and 120 days of cyclosporine

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administration, their study demonstrated a significant GO increase in the buccal mucosa and relevant tissues, an increase in osteoclastic activity and a decrease in osteal density (Spolidorio et al, 2004).

Kim et al showed that TGF-ß1 has an essential role in the cell proliferation associated with pathophysiological states (such as GO) and that the transcription of TGF-ß1 is regulated by CsA. This same study further proposed that in CsA-stimulated GO, the diminishing proteolytic activity of gingival fibroblasts is supported by TGF-ß1 (Kim et al, 2008).

In renal transplant patients, the severity of GO is influenced by several risk factors, such as the serum or salivary concentration, drug formulation, dosage, duration of intake, time since transplantation, patient age, patient sex, concurrent medications being administered and the patients' oral hygiene status (Seymour et al, 2000; Thomason et al, 2005).

Seyrafi et al studied Iranian graft recipients and demonstrated a correlation between cyclosporine treatment and GO (Seyrafi et al., 1999). This observation was also mirrored by the study of Baharvand and Ranjbar-Pazooki, who reported higher rates of GO in younger patients and also along with the simultaneous use of cyclosporine and calcium channel blockers (Baharvand and Ranjbar, 2002).

Numerous therapeutic methodologies have been suggested in the management of GO, ranging from the implementation of oral hygiene programmes, surgical interventions and/or alternate pharmacological therapy (Ciavarella et al, 2007).

'Improvement' in GO has been reported by several studies that have advocated novel immunosuppressant drugs, such as tacrolimus, rapamycin RS and mycophenolatemofetil. However, their collateral effects are still not broadly reported. Accordingly, CsA remains the most commonly used drug in transplant recipients. Nevertheless, there is evidence that fewer oral side effects are associated with tacrolimus than CsA (Chand et al, 2001; Verma and Dhawan, 2005).

The rationale of the current study was that TGF-β1 represents the mechanism of action of CsA. In addition, TGF-β1 is the key determinant of GO because it stimulates fibroblast proliferation and extracellular matrix production.

The aim of this case-control study was to compare the TGF-β1 level between renal transplant recipients who had been prescribed cyclosporine and experienced gingival enlargement and others who were taking cyclosporine but were without gingival enlargement.

2. Materials and methods

A centre-based case-control study was conducted at two renal transplant centres to measure and compare the TGF-β1 levels in CsA-stimulated GO in renal transplant recipients with that of patients taking CsA who did not exhibit gingival enlargement.

Eighty participants who had been prescribed CsA and were both with and without GO were included in the study and were equally divided two groups: 40 participants in the study group who were using CsA and who had been diagnosed with GO, and 40 matched participants in the control group who were also using CsA but were without GO. The study and control groups were matched for potential risk factors that included the CsA dose and duration, age, sex and time since renal transplantation.

Data were collected from the patients' medical records regarding age, gender, immunosuppressive regimen with dosage (mg/kg), duration of treatment (months) of each immunosuppressive drug and type of administered antihypertensive treatment.

The inclusion criteria included renal transplant patients of both genders who were currently taking CsA and had stable renal function as defined by serum levels of creatinine < 2 mg/dl.

Patients taking any other medications and/or who had been diagnosed with any other condition known to cause gingival enlargement (e.g. nifedipine), who were mouth breathers, who had an open bite, who were pregnant or who had been diagnosed with any systemic diseases, such as diabetes mellitus, cardiovascular disease or epilepsy were excluded. The exclusion criteria also included edentulous patients, those who had experienced rejection episodes or patients who had undergone any type of periodontal treatment or had taken antibiotics for any known infections during the preceding three months before the study began.

A full-mouth periodontal examination was conducted using the Plaque Index (PI, Silness and Löe 1964), the Gingival Index (GI, Löe and Silness 1963), the probing pocket depth (PPD) and the Clinical Attachment Loss (CAL, Glavind and Löe 1967). The periodontal parameters were assessed for each participant at six sites per tooth (mesiobuccal, buccal, distobuccal, mesiolingual, lingual, and distolingual) with a graduated William's periodontal probe.

The extent of the gingival enlargement was measured using the McGraw Index (Pakosz et al., 2012) as follows.

1: No gingival enlargement
2: Gingival enlargement only in the interdental papilla
3: Gingival enlargement covering less than one-third of the dental crown
4: Gingival enlargement covering more than one-third of the dental crown

2.1. Cytokine measurement

Five millilitres of blood were drawn from the antecubital vein from all participants. The blood samples were centrifuged at 3000 rpm for 10 min, and the collected serum was frozen at −80 °C. The serum TGF-β1 levels were determined by enzyme-linked immune-sorbent assay kit according to the manufacturer's instructions (BD Company[1]).

Each plate was treated with 100 µl of anti-human cytokine diluted in phosphate buffered saline (PBS). After sealing, the plates were incubated overnight at room temperature, and then the plates were aspirated and washed to eliminate free antigens by filling each plate with 400 µl washing buffer (0.05% Tween®20 in PBS, PH 7.2–7.4). The plates were then blocked, sealed and re-incubated for an hour at room temperature.

Next, 100 µl per well of standard reagent diluent were added to act as the detection antibody. The plates were resealed and incubated at room temperature for an additional hour. To eliminate unbound cytokines and other components of the samples, the plates were systematically aspirated and washed seven times as previously described.

[1] Becton, Dickinson Company, https://www.bdbiosciences.com.

Subsequently, the quantitative determination of the number of tested cytokines in the samples was carried out by adding 100 µl of the substrate solution to each well. A colour reaction was induced by adding 100 µl of tetramethylbenzene. This reaction produces a colour change only in wells that contain the specific target cytokine. The colour reaction was permitted to develop in the dark at room temperature for at least 20 min and was ended by adding 50 µl of 2 N sulphuric acid. Finally, the optical densities were measured at a wavelength of 450 nm by employing a microplate reader.

3. Results

Eighty renal transplant recipients taking CsA as their primary immunosuppressant were enrolled in the study. The participants' mean age was 46 ± 12.41 years, and the age range fell between 20 and 77 years.

The participants were grouped into five age groups: 20–29 years, 30–39 years, 40–49 years, 50–59 years and those >60 years. Most participants were in the 50–59-year age group in both the study and control groups. Seventy-five percent of the participants were males. The mean number of years since the transplantation was 7.23 ± 4.20 years for the study group and 6.45 ± 3.80 years in the control group.

The study group showed a higher and also a strong statistically significant (P-value: 0.0001) mean serum CsA level of 148.16 ± 40.30 ng/dl compared to the control group (103.13 ± 18.35 ng/dl). The mean serum TGF-ß1 result in the study group was 17.11 ± 23.70 ng/ml, which was significantly higher than that of the control group (8.62 ± 12.97 ng/ml). However, the mean serum creatinine level in the study group was statistically insignificant at 1.15 ± 0.38 mg/dl (P-value: 0.213) in comparison with the control group, which was 1.25 ± 0.37 mg/dl Table 1.

The mean PI score for the study group was 1.13 ± 0.38 and was statistically significant (P-value: 0.049) when compared to the control group (0.96 ± 0.39). The mean GI score for the study group was 1.31 ± 0.39, while it was 1.13 ± 0.46 in the control group, which was statistically insignificant. The PPD measurements for the study and control groups were 0.14 ± 0.20 and 0.18 ± 0.26, respectively. Further, the mean clinical attachment loss values for the study and control groups were 0.07 ± 0.11 and 0.09 ± 0.13, respectively Table 2.

The participants with Grade-I GO had a mean serum TGF-β1 of 12.99 ± 23.13 ng/dl, while those with Grade-II GO had a mean serum TGF-β1 of 13.3 ± 15.45 ng/dl. Participants with Grade-III GO had a mean serum TGF-β1 of 53.06 ± 24.7 ng/dl. A comparison of the different grades of gingival overgrowth was statistically significant (P-value: 0.004) Table 3.

Table 1 Distribution of serum CsA, serum creatinine and serum TGF-β1 values in the study and control groups.

Serum levels	Study group	Control group	P-value
	Mean (±SD)	Mean (±SD)	
S. CsA	148.16 (±40.30)	103.13 (±18.35)	0.0001**
S. Creatinine	1.15 (±0.38)	1.25 (±0.37)	0.213
S. TGF-β1	17.11 (±23.70)	8.62 (±12.97)	0.05*

** P-value is strongly statistically significant.
* P-value is statistically significant.

Table 2 The periodontal parameters of the study and control groups.

Periodontal parameters	Study group	Control group	P value
	Mean (±SD)	Mean (±SD)	
PI	1.13 (±0.38)	0.96 (±0.39)	0.049*
GI	1.31 (±0.39)	1.13 (±0.46)	0.056
PPD	0.14 (±0.20)	0.18 (±0.26)	0.417
CAL	0.07 (±0.11)	0.09 (±0.13)	0.465

* P-value is statistically significant.

Table 3 Correlation between the mean serum TGF-β1 and the grade of gingival overgrowth.

Grade of gingival overgrowth	N	Mean (±SD)	P-value
Grade I	22	12.99 (±23.13)	0.004*
Grade II	14	13.3 (±15.45)	
Grade III	4	53.06 (±24.7)	
Total	40	17.11 (±23.7)	

**P-value is significant, one-way analysis of variance test performed.

4. Discussion

CsA has been almost exclusively used in the prevention of organ transplant rejection. One unique odontological side effect of CsA is the occurrence of GO.

GO may induce emotional as well as social problems for the individual due to the aesthetically unpleasant disfigurement, which is often misjudged even by health professionals. Furthermore, Peters et al suggested that the health-related quality of life following transplantation seems to be impaired (Peters et al., 2004).

The significantly higher mean TGF-β1 level in the study group compared to the control group suggests that this growth factor may play a part in the accumulation of the extracellular matrix. A genetic predisposition may also influence a variety of factors in drug-induced GO, such as gingival fibroblast formation, functional heterogeneity and both an increase and a decrease in collagenolytic activity, drug metabolism and collagen synthesis.

Yoshida et al argued in favour of TGF-ß1 in CsA-induced GO and claimed that higher levels of specific cytokines, especially TGF-β1, are the result of a multi-functional inflammatory mediator; their study suggested that this mediator participates in the build-up of the extracellular matrix along with collagenous proteins (Yoshida et al, 2005).

Several studies have suggested that the majority of cells may express TGF-β1 isoforms in addition to endothelial cells fibroblasts and gingival inflammatory cells (Condé et al, 2009; Wright et al, 2001). An immunohistochemical study on phenytoin and nifedipine-induced and cyclosporine GO indicated higher levels of gingival TGF-ß1 and TGF-ß2 (24), which has also been mirrored by several other studies in which there were higher levels of specific cytokines (especially TGF-β1) as a multifunctional inflammatory mediator (James et al, 2010; Ruhl et al, 2004; Yoshida et al, 2005). These studies

suggested that TGF-β1 participates in the build-up of the extracellular matrix.

In the literature, the normal value of TGF-β1 has varied. Studies have reported a mean value of TGF-β1 in normal healthy individuals between 3.8 ± 2.9 ng/ml (Cuhaci et al, 1999; Wunderlich et al, 1998). In the present study, the mean TGF-β1 level in the control group when compared to the values outlined in previous studies was found to be slightly higher than that of healthy individuals not taking any CsA and without GO. This difference has been accredited to higher serum CsA levels in the control group compared to healthy levels, but these levels were not at a high enough level to induce GO.

Within the study group, a significant correlation between the TGF- ß1 level and the degree of GO was demonstrated. Participants with Grade-I GO had a TGF-ß1 level of 12.99 ng/ml, while those with Grade-II GO showed a TGF-ß1 level of 13.3 ng/ml; finally, participants with Grade-III GO demonstrated a TGF-β1 level of 53.06 ng/ml. It has been shown that the greater the TGF-ß1 level, the more severe the degree of GO (Dias Corrêa et al, 2011; Saito et al, 1999). The degrees of inflammation, fibrosis and cellularity depend on the duration, dose and identity of the drug and also the quality of the patient's oral hygiene.

4.1. Limitations

This study had several limitations. First, gingival enlargement typically occurs during the first year after commencing the use of an immunosuppressive treatment. Since our study was a cross-sectional study, we were not able to comment on the exact occurrence of GO following immunosuppressive treatment and its recurrence rate. Another limitation was that the sample size was not large enough to represent the entire CsA drug-induced GO population, so our findings cannot be generalised to any other groups.

5. Conclusion

This study was conducted to investigate the TGF-ß1 profile in renal transplant patients taking CsA; the results revealed significantly elevated levels of serum TGF-ß1 in participants who demonstrated CsA-induced gingival enlargement.

Our findings also indicated that increases in the degree of GO occur along with an increase in TGF-β1 levels. This result provides additional evidence regarding the level of TGF-ß1 and its association with GO and suggests that TGF-ß1 may be considered a useful marker of GO. The serum TGF-ß1 is also likely not the only factor accountable for CsA-induced GO. Further studies should attempt to identify other contributing factors. Finally, a complex collaboration between inflammatory mediators and tissue modelling is likely implicated in the pathogenic mechanisms of this result.

5.1. Recommendations

1. Further investigations are necessary to determine the exact role of TGF-β1 on fibroblasts and its mechanism of action in the process of GO.
2. The administration of CsA is beyond the control of the dental professional, and the feasibility of discontinuing the drug and replacing it with a suitable alternative should be discussed with the prescribing physician. After such replacement, spontaneous regression may occur within 12 months if the patient maintains good oral hygiene.
3. Patients who are at risk for or who have already developed GO will benefit from effective oral hygiene measures to reduce the inflammatory component in their gingival tissues.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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