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Review article

Risk factors for drug-induced gingival overgrowth

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Abstract

Background/Aims: Drug-induced gingival overgrowth remains a significant problem for the periodontologist. Many patients medicated with the drugs implicated in this unwanted effect experience significant, recurrent gingival problems that require repeated surgical excisions. In this review, we attempt to identify and quantify the various "risk factors" associated with both the development and expression of the drug-induced gingival changes.

Method: The risk factors appraised include age, sex, drug variables, concomitant medication, periodontal variables and genetic factors. Elucidation of such factors may help to identify "at risk patients" and then develop appropriate treatment strategies.

Results: Of the factors identified, the only one that can be affected by the periodontologist is the patents' periodontal condition. However, drug variables and concomitant medication do impact upon the expression of gingival overgrowth.

Conclusion: The identificatioin of risk factors associated with both the prevalence and severity of drug-induced gingival overgrowth is important for all parties involved with this unwanted effect. Both periodontologist and patient have an important rôle to play in improving oral hygiene and gingival health. Likewise, there is always an opportinity to establish a close liaison between the patient's physician and the periodontologist to try and identify alternative drug regimens that can help reduce the impact of this unwanted effect.

Key words: drug-induced gingival overgrowth; risk factors; phenytoin; cyclosporin; calculus channel blocker

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Most articles on drug-induced gingival overgrowth make reference to the prevalence of this unwanted effect in relation to the particular drug or groups of drugs implicated. For phenytoin, the figure of 50% is often quoted (Angelopoulous & Goaz 1972) whereas for cyclosporin and the calcium channel blockers, a much lower prevalence of 30% and 10% respectively is reported (Barclay et al. 1992, Ellis et al. 1999, Seymour et al. 1987) thus, it would appear that there is a variable gingival response in patients taking these drugs. Indeed, the term "responders" and "non-responders" appear in the literature. Furthermore, within the group of patients that develop this unwanted effect, there appears to be variability in the extent and severity of the gingival changes. The term "clinically significant overgrowth" has been applied to those patients whose gingival changes require surgical intervention to restore gingival contour (Thomason et al. 1993). It would seem pertinent to identify and explore possible risk factors relating to both the prevalence and severity of drug-induced gingival overgrowth that have been reported in the literature.

The aim of this paper is to appraise the various risk factors that have been elucidated for drug-induced gingival overgrowth. Identifiable factors can be considered under the following headings: age and other demographic factors; drug variables; concomitant medication; periodontal variables and genetic factors.

Age and Other Demographic Variables

Age has been considered an important risk factor for drug-induced gingival overgrowth with particular reference to phenytoin and cyclosporin (Daley et al. 1986, Esterberg & White 1945, Hefti et al. 1994, Kapur et al. 1973, Schulz et al. 1990). Early studies on the prevalence of phenytoin-induced gingival overgrowth identified that teenagers were particularly at risk from this unwanted effect (for review, see Hassell (1981)).

Many of these studies could be criticised for the sampling technique (i.e. hospitalised or institutionalised patients) and as such did not represent a true reflection of the problem. Two community-based studies (Casetta et al. 1997, Thomason et al. 1992) have reported a lower prevalence of phenytoin-induced gingival overgrowth (13% and 40% respectively). Although age was not reported as a significant risk factor per se, the first of these studies was based on a relatively young population with a mean age of 40.6 years (Thomason et al. 1992) and in the latter (Casetta et al. 1997) it was reported that the combination of younger age and poor oral hygiene seemed to predispose to the severest level of gingival involvement.

Age has been reported as a risk factor for cyclosporin-induced gingival overgrowth (Daley et al. 1986, Hefti et al. 1994, Schulz et al. 1990, Somacarrera et al. 1994). These observations are supported by animal studies (Kitamura et al. 1990, Morisaki et al. 1993). Other studies have looked specifically at the prevalence of gingival overgrowth in paediatric organ transplant patients (Allman et al. 1994, Karpinia et al. 1996, Kilpatrick et al. 1997, Lowry et al. 1995). Nearly all the patients from these studies showed some form of gingival changes and the number of children with clinically significant gingival overgrowth was higher (52%) when compared to adults.

Age is not an applicable risk factor for the calcium channel blockers since the use of these drugs is usually confined to the middle aged and older adult. This is supported by a recent study of more than 800 patients medicated with calcium channel blockers where age was not identified as a significant risk factor (Ellis et al. 1999). The patients in this study were in the older age group with a median age of 63 years. Nevertheless, in patients medicated with both cyclosporin and calcium channel blockers, age has been identified as a risk factor (Thomason et al. 1997). Indeed it has been suggested that the differences in the prevalence of the overgrowth induced by these different drugs reflects the different age groups at which they are targeted (Hassell & Hefti 1991); phenytoin being targeted mainly at the young, calcium channel blockers at the post middle aged and cyclosporin across a broad range of ages. The evidence supporting age as a risk factor especially with respect to cyclosporin-treated patients, is now convincing. One possible explanation for this association may reside with an interaction between circulating androgens and gingival fibroblasts. Such cells can readily metabolise testosterone to the active metabolise 5 α-dihydrotestosterone. Phenytoin enhances this metabolism (Sooriyamoorthy et al. 1988), and excised tissue from both cyclosporin and nifedipine-induced gingival overgrowth exhibits a similar increase in androgen metabolism (Sooriyamoorthy et al. 1990). Circulating androgen levels will be higher in adolescents and teenagers, and the active metabolite could act on sub-populations of gingival fibroblasts and cause either an increase in collagen synthesis and/or a decrease in collagenase activity.

Other Demographic Variabies

Very few studies have investigated whether gender is a risk factor for drug-induced gingival overgrowth. In a review of the phenytoin studies, Hassell reported that gender and race were not important risk factors for the expression of gingival (Hassell 1981).

Many of the cyclosporin studies have a significant male bias since organ transplantation (especially heart transplants) is more frequently carried out on men. Some report higher gingival overgrowth scores in males (King et al. 1993, Montebugnoli et al. 1996) but differences were not statistically significant. Two further (Thomason et al. 1995, Thomason et al. 1996b) used stepwise regression techniques to disentangle the effects of a range of risk factors. Both studies showed that males were at greater risk from developing this unwanted effect than females and that the severity of the changes would be greater in men. Similarly males were shown to be 3 times more likely than females to develop clinically significant gingival changes when medicated with calcium channel blockers (Ellis et al. 1999) ($p=0.023$). Evidence from animal studies also supports this finding, with male rats being more prone to drug-induced gingival overgrowth than females (Ishida et al. 1995). It was suggested that there existed a serum threshold above which overgrowth occurs, and that this level was lower in males.

There is increasing evidence with respect to both cyclosporin and the calcium channel blockers that males are more prone to developing gingival overgrowth than females and that the gingival changes are more severe. Whether this relates to existing periodontal factors, pharmacological variables or a hormonal co-factor remains to be determined.

Drug Variables

The relationship between the extent and severity of gingival overgrowth and a variety of drug variables (i.e., dose, duration, serum and salivary concentrations) remains an area of controversy. Much of the variability from the studies relates to the method of assessing gingival overgrowth, the timing of the blood sample, the number of patients being studied and the elucidation of other factors than can impact upon a drug's pharmacokinetic profile. Most would agree that some baseline or threshold concentration of the drug is required to initiate the gingival changes and that such a threshold concentration may vary from individual to individual.

Drug dosage tends to be a poor predictor of the gingival changes (for review, see Seymour & Heasman (1988), Seymour & Jacobs (1992)). It would be more appropriate to relate dose to the patient's body weight to obtain a more meaningful interpretation of dosage and its relationship to gingival overgrowth. Many studies have also investigated the relationship between serum concentrations of the implicated drug and the expression of gingival overgrowth. Both phenytoin and calcium channel blockers obtain steady state therapeutic drug levels at 7–10 days after the initiation of therapy. Thus for these two drugs a serum sample at any time point is likely to be a true reflection of the drug's concentration. Cyclosporin measures are often taken as the so-called trough concentrations. Whilst such single measures are useful for checking compliance, the level of anticonvulsant activity or immunosuppression, they only reflect one aspect of the drug's pharmacokinetic profile. Other pharmacokinetic measures that may be more pertinent in relation to gingival overgrowth include bioavailability, degree of protein binding, volume of distribution, and an overall assessment of drug concentration in relation to time. This latter method is referred to as area under the plasma/serum concentration

time curve (AUC) and is a measure of the total concentration of the drug over a specific time period. Such a measure requires repeated sampling which is often impractical in large epidemiological studies. Single serum measures are easy to obtain and often available as part of the patient's ongoing medical care. Thus, the lack of any clear relationship between serum or blood concentrations of the drug with the expression of gingival overgrowth may be a reflection of the shortfall of the sampling technique or a lack of investigation into more appropriate pharmacokinetic vanables.

The type of cyclosporin preparation may well have some impact on the development of gingival overgrowth in organ transplant patients (Wondimu et al. 1996). In this study cyclosporin was given as a solution (mixed with milk) or in capsule form. The effects of both preparations on the gingival tissues was compared during a one year longitudinal study. Gingival overgrowth was observed in 37% of the patients taking the cyclosporin solution, compared to 43% dosed with capsules. However, the solution patients showed an earlier onset of gingival changes and more extensive overgrowth than those medicated with capsules. It was concluded that changing a patient's cyclosporin medication from a solution to capsules might minimise the development of gingival overgrowth. In this study the different effects of the two cyclosporin preparations on the gingival tissues may be related to subsequent changes in the drug's pharmacokinetics, in particular bioavailability and time to maximum blood concentrations. Alternatively, it has been reported that cyclosporin levels in whole saliva are much higher in subjects who take the drug in liquid form as opposed to capsules (Modeer et al. 1992). Whether local concentrations of cyclosporin plays a role in the development of gingival overgrowth remains speculative (see later).

Both phenytoin and cyclosporin are secreted in saliva, and several studies have investigated whether salivary concentrations of these drugs are important determinants for gingival overgrowth. As with serum concentrations there is no clear picture. For phenytoin, some studies have reported that salivary concentrations are positively correlated with gingival overgrowth (Babcock & Nelson 1964, Conard et al. 1974, Hassell et al. 1983), whilst others have failed to confirm such a relationship (Ball et al. 1996, Dahllof & Modeer 1986, Modeer & Dahllof 1987). It is possible that the concentration of phenytoin or its major metabolite (HPPH) present in saliva are not representative of those present at the site of action, that is, the gingival tissue itself.

Salivary concentrations of cyclosporin in relation to gingival overgrowth present a similar situation to phenytoin. A positive correlation has been found between cyclosporin concentrations in stimulated saliva and the extent of gingival overgrowth (Daley et al. 1986, Hefti et al. 1994, McGaw et al. 1987). Other studies, however, have reported a lack of correlation between unstimulated salivary cyclosporin levels and gingival overgrowth (King et al. 1993). These conflicting findings may be explained by the fact that dental plaque may act as a reservoir for cyclosporin, which is then released by the actions of stimulated salivary flow (Niimi et al. 1990). Thus, whilst salivary samples are easy to collect, they may not be as useful an indicator for the development of gingival overgrowth.

Local concentrations of both phenytoin and the dihydropyridine class of calcium channel blockers in gingival crevicular fluid (GCF) have provided some useful insight into local tissue activity (Ellis et al. 1992, McLaughlin et al. 1995, Seymour et al. 1994). GCF concentrations of phenytoin do not appear to be related to the extent of gingival overgrowth (McLaughlin et al. 1995). However, significant sequestration of both nifedipine and amlodipine has been observed in patients who exhibit significant gingival changes arising from these drugs (Ellis et al. 1992, Seymour et al. 1994). Nevertheless, the effect of a range of nifedipine variables on the severity of gingival changes in organ transplant patients has been investigated (Thomason et al. 1997). Despite the high levels of nifedipine sequestered in the GCF only the plasma concentration of nifedipine was identified as a risk factor for the severity of the gingival changes. As such the mechanism of the drug sequestration and its relationship to the gingival changes remains unknown.

Concomitant Medication

The 3 major categories of drug that are implicated in gingival overgrowth are seldom the only medication prescribed to the patient. The effect of polypharmacy has been studied in relation to both cyclosporin and phenytoin-induced gingival overgrowth.

There is now a considerable body of evidence that the combination of nifedipine and cyclosporin in organ transplant patients produces more gingival overgrowth than if either drug was used singularly (Bokenkamp et al. 1994, Margiotta et al. 1996, O'Valle et al. 1995, Thomason et al. 1995, Thomason et al. 1996, Thomason et al. 1993, Wilson et al. 1998, Wondimu et al. 1996). It has been suggested that combined therapy may increase the prevalence of the condition but not the severity (Pernu et al. 1993b). The same authors suggested that combined treatment was a significant risk factor for progression and recurrence of the lesion after treatment (Pernu et al. 1993a). In a study with small patient groups, King and colleagues suggested that overgrowth was not potentiated by concomitant medication with a dihydropyridine (King et al. 1993). Similar results were reported for the effect of an alternative calcium channel blocker, verapamil. Both the prevalence of the condition and the severity of the changes were greater in the combined group but the differences were not statistically significant (Cebeci et al. 1996b).

Other drugs taken by organ transplant patients could well influence the expression of gingival overgrowth (Wilson et al. 1998). In adult organ transplant patients, dosages of both prednisolone and azathioprine appeared to afford the patients some degree of "protection" against the development of gingival overgrowth, whereas in children dosing with azathioprine did likewise. Other studies have shown that both azathioprine and prednisolone reduce the severity of drug-induced gingival overgrowth in organ transplant patients (Hassell & Hefti 1991, Somacarrera et al. 1994). The so-called protective effect of these two drugs on gingival overgrowth may arise from their anti-inflammatory actions on plaque-induced gingival inflammation. The latter factor certainly appears to have a significant impact on the extent and severity of the drug-induced gingival changes.

Polypharmacy can have an effect on phenytoin-induced gingival overgrowth (Maguire et al. 1986). Phenytoin is metabolised (hydrolysed) in the liver by P450 enzymes to 5-(4-hydroxyphenyl)-

5-phenylhydantoin (4-HPPH). This metabolite has been shown to induce gingival overgrowth in cats (Hassell & Page 1978). Anticonvulsants such as phenobarbitone, primidone and carbamazepine have been shown to induce hepatic P450 isoenzyme and if given in conjunction with phenytoin will increase serum concentrations of 4-HPPH. This may explain the increased prevalence of gingival overgrowth in patients receiving multiple anticonvulsant therapy.

Periodontal Variables

Plaque scores and gingival inflammation appear to exacerbate the expression of drug-induced gingival overgrowth, irrespective of the initiating drug (for review, see Seymour (1991), Seymour & Heasman (1988), Seymour & Jacobs (1992)). Such findings may suggest causality with a patients oral hygiene being a significant risk factor for the expression of drug-induced gingival overgrowth (Ellis et al. 1999, King et al. 1993, Pernu et al. 1992, Somacarrera et al. 1994, Thomason et al. 1995, Thomason et al. 1996, Thomason et al. 1993) although contrary reports have also appeared (Schulz et al. 1990, Seymour et al. 1987, Wondimu et al. 1993). Furthermore, most of the evidence to support a relationship between bacterial plaque and gingival overgrowth has been derived from cross-sectional studies, and it is not clear whether plaque is a contributory factor or a consequence of the gingival changes. However, in circumstances when other additional structures such as orthodontic appliances impede cleaning then the prevalence of overgrowth is high (Daley et al. 1991). The effect of an oral hygiene programme on cyclosporin-induced gingival overgrowth was examined in a longitudinal trial (Seymour & Smith 1991). Both the oral hygiene and the control group developed significant gingival changes over the 6-month post-transplant investigation period, although the magnitude of the changes in the oral hygiene group was less marked. Oral hygiene therapy, whilst of some benefit to the patients, failed to prevent the development of gingival overgrowth. An improvement in oral hygiene during the first 6 months post transplant period has also been reported in a more recent study of 100 organ transplant patients (Somacarrera et al. 1994). Despite the improvement in oral hygiene from base line values, overgrowth was still seen in 43% of cases and the plaque index and gingivitis scores showed a significant correlation with gingival enlargement. Stone and co-workers reported a high incidence of gingival overgrowth (36%) in a control group of 50 multiple sclerosis patients not taking cyclosporin (Stone et al. 1989). This was attributed to compromised manual dexterity common in these patients and the report illustrates that the changes seen in the contour of gingival tissue in all patients can be due to factors other than their drug therapy. Taking the findings as a whole, it would be reasonable to suggest that proper oral hygiene might be expected to minimise the severity of cyclosporin-induced gingival overgrowth, possibly by eliminating the inflammatory component of the lesion. Improved oral hygiene in itself would not appear to prevent overgrowth.

Investigations have been carried out to elucidate whether a patient's periodontal status prior to appropriate drug therapy relates to the development of gingival overgrowth. As previous, these studies have focussed on organ transplant patients. In a group of renal transplant patients, the presence of gingival bleeding increased significantly the risk of developing gingival overgrowth (Pernu et al. 1992). This study also showed that the occurrence of gingival overgrowth was significantly related to the simultaneous presence of plaque and subgingival calculus. However, both of these factors did not increase the risk of overgrowth. A more recent study (Varga et al. 1998) has evaluated the impact of a patient's periodontal condition prior to organ transplantation on the development of gingival overgrowth post transplant. Their results showed that patients who exhibited a hyperplastic gingivitis prior to transplant were highly likely to develop severe gingival changes post-transplant. This would suggest a "susceptibility" of the gingival tissues (or fibroblasts) to both plaque-induced inflammatory changes and cyclosporin.

Periodontal variables in particular plaque and gingival inflammation are also important risk factors for the expression of gingival overgrowth attributable to the calcium channel blockers. As with many of the previous studies, evidence has been obtained from cross-sectional studies (Bullon et al. 1995, Bullon et al. 1996, Neumann et al. 1996, Tavassoli et al. 1998). There seems to be agreement that the extent of gingival inflammation appears to be an important risk factor for the expression of gingival overgrowth in relation to the calcium channel blockers. It is interesting to note that gingival changes are more pronounced in patients taking nifedipine for cardiovascular disorders compared to those taking these drugs whilst under haemodialysis.

Genetic Factor

Fibroblast heterogeneity remains one of the key factors used to explain the variable response of the gingival tissues to the various gingival overgrowth-inducing drugs. However, whilst this may be a useful in vitro explanation, it has limited clinical value in identifying "at risk patients". There is no clinical marker of gingival fibroblast phenotype. A genetic predisposition could influence the metabolism of phenytoin, cyclosporin and nifedipine, since all three drugs are metabolised by the hepatic cytochrome P450 enzymes. Cytochrome P450 genes exhibit considerable polymorphism which results in inter-individual variation in enzyme activity. This inherited variation in metabolism of the offending drug may influence the patients serum and tissue concentrations and hence their gingival response. Whilst cytochrome P450 variation may be a risk factor for drug-induced gingival overgrowth it is totally impractical to assess this on a clinical basis.

The one genetic marker that has been investigated in relation to drug-induced gingival overgrowth is the human lymphocyte antigen expression (HLA). Investigation of this marker has been confined to the organ transplant patients since their HLA phenotype is determined prior to transplantation. Several studies have reported on the relationship between HLA expression and the incidence of drug induced gingival overgrowth (Cebeci et al. 1996a, Margiotta et al. 1996, Pernu et al. 1994, Thomason et al. 1996b).

One study reported that patients who expressed HLA-DR1 are afforded some degree of protection against gingival overgrowth whilst HLA-DR2 may increase the development of this unwanted effect (Pernu et al. 1994). Unfortunately no attempt was made to correct for the effects of multiple significance testing or to disintangle the ef-

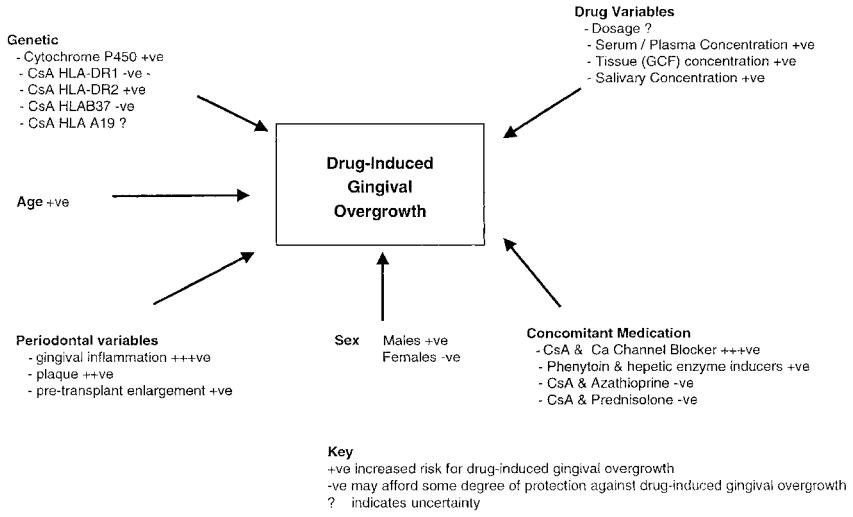

Fig. 1. Overview of identified factors that may contribute to the expression of drug-induced gingival overgrowth.

fects of the different medication regimens. However, the suggestion of a protective role for HLA-DR1 gained some support 2 years later (Cebeci et al. 1996a) but again no attempt was made to control for the effect of multiple significance testing. Independent validation of the effect of HLA-DR2 has been reported when correction was made for other known risk factors. Nevertheless, after controlling for the effect of multiple significance testing the relationship was not significant at the 5% level (Thomason et al. 1996).

A trend towards an increased presence of HLA-A19 antigen has also been reported although the relationship was not significant after correction for multiple significance testing (Margiotta et al. 1996). To date only HLA-B37 has been identified as a significant risk factor after correction for the effect of multiple significance testing and these patients are protected in some way from the effects of gingival overgrowth (Thomason et al. 1996). The mechanism that may tie HLA antigens to gingival overgrowth are unclear. The concept of molecular mimicry in the wider field of periodontal disease (Klouda et al. 1986) or an effect on lymphocyte function (Pernu et al. 1994) have been postulated. The apparent HLA associations may represent nothing more than tight linkage disequilibrium between HLA and non HLA genes in the MCH region of human chromosome 6 (Lechler 1994).

Conclusion

Risk factors for any condition are only meaningful if they exhibit both reliability and sensitivity. For the patients perspective they would want to know the likelihood of developing drug-induced gingival overgrowth when starting their medication. For the clinician this information is likewise valuable, but in addition they would want to know whether this unwanted effect is going to recur on a regular basis and hence require further surgical intervention. This will have implications for all parties and in particular the resources required to treat the patient effectively. Thus risk factors and their identification are very pertinent when they are related to treatment.

The 3 main categories of drugs that cause gingival overgrowth are prescribed invariably for the rest of the patient's life. If any one of the drugs causes troublesome, recurrent gingival overgrowth there does not appear to be a great deal of scope in changing the patient's medication. 6 'risk factors' have been identified from the literature and these are summarised in Fig. 1. However, whilst it is possible to identify the severity of these effects relative to each other within a study, it is not possible to rank these or provide additional weighting for observations from different studies. Over the past 50 years, 3 main drugs have been implicated in causing gingival overgrowth. 2 of these (cyclosporin and the calcium channel blockers) were identified in the last two decades. The usage of these drugs is going to increase and other drugs may be added to this list. Thus, the problem of drug-induced gingival overgrowth is also going to increase. This highlights the need to identify the patient at risk from this unwanted effect and developing the appropriate management strategies.

Zusammenfassung

Risikofaktoren für medikamentös bedingte fibröse Gingivahyperplasie

Die medikamentös bedingte fibröse Gingivahyperplasie ist immer noch ein erhebliches Problem für den Parodontologen. Viele Patienten, die Medikamente mit dieser unerwünschten Arzneimittelwirkung einnehmen, haben erhebliche wiederkehrende parodontale Probleme, die wiederholte chirurgische Eingriffe erforderlich machen. In dieser Übersicht sollen die verschiedenen Risikofaktoren identifiziert und bewertet werden, die mit der Entwicklung und Ausprägung dieser medikamentös bedingten parodontalen Veränderungen in Verbindung gebracht werden. Zu diesen Risikofaktoren gehören Alter, Geschlecht, pharmakologische Parameter, zusätzliche Medikation, parodontale Parameter und genetische Faktoren. Die Aufklärung solcher Faktoren könnte dabei helfen, Risikopatienten zu identifizieren und dementsprechende Therapiestrategien zu entwickeln. Von den identifizierten Faktoren ist der parodontale Zustand des Patienten der einzige, der von einem Parodontologen beeinflußt werden kann. Dennoch beeinflussen pharmakologische Parameter und zusätzliche Medikation die Ausprägung der Gingivahyperplasie. Deshalb erscheint eine enge Zusammenarbeit zwischen dem Arzt und dem Parodontologen des Patienten mit dem Ziel alternative Medikationen zu versuchen, die die parodontale Situation des Patienten weniger ungünstig beeinflussen, als sinnvoll.

Résumé

Facteurs de risque dans l'hyperplasie gingivale médicamenteuse

L'hyperplasie gingivale médicamenteuse demeure un important problème pour le parodontologue. De nombreux patients traités par les médicaments causant cet effet indésirable éprouvent d'importants problèmes gingivaux récurrents, qui rendent nécessaires des excisions chirurgicales répétées. Dans la présente revue, nous tentons d'identifier et de définir quantitativement les différents facteurs de risque associés au développement des altérations gingivales d'origine médicamenteuse ainsi qu'à leur expression. Les facteurs de risques évalués comprennent l'âge, le sexe, les variables concernant le médicament, les médications concomitantes, les variables

parodontales et les facteurs génétiques. En portant la lumière sur les facteurs de ce type, on peut contribuer à identifier les "patients à risque" et à mettre au point des stratégies thérapeutiques. Parmi les facteurs identifiés, le seul sur lequel le parodontologue peut agir est l'état parodontal du patient. Cependant, les variables concernant le médicament et les médications concomitantes ont une influence sur l'expression de l'hyperplasie gingivale. Cela indique la possibilité d'établir une liaison étroite entre le médecin des patients et leur parodontologue, pour essayer et identifier des alternatives de traitement pouvant améliorer leur état gingival.

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