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ORIGINAL ARTICLE

Lip impressions: a new method for monitoring morphological changes in orofacial granulomatosis

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AIM: To develop and evaluate an objective method for assessing lip size and treatment-related morphological changes in orofacial granulomatosis (OFG) patients.
MATERIALS AND METHODS: Patients with swollen lips because of OFG ($n = 21$) were enrolled. A light-body polyvinylsiloxane material was used to take lip impressions before and after treatment ($n = 10$), or during treatment ($n = 11$). Plaster models were cast from the impressions and the lips were measured using callipers. The intra-examiner and inter-examiner reproducibility of the technique were assessed.
RESULTS: OFG patients had significantly larger lips than controls ($P < 0.0001$). The coefficient of variation on repeated measurements of the same impression was 1.6% and for duplicate impressions was 2.6%. Significant reduction in lip size was shown in all 10 patients after diet restriction ($P < 0.002$). Seven of 11 patients whose impressions were taken at least 3 months after the initiation of cinnamon- and benzoate-free diet also showed reduction in lip size during follow up ($P < 0.002$).
CONCLUSIONS: Serial lip impressions appear to be reliable for routine quantification of morphological changes of the lips in OFG patients. We present a new reproducible and sensitive method for assessing changes in lip size in response to treatment in OFG.
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Keywords: orofacial granulomatosis; lip morphology; lip impressions; cinnamon and benzoate free diet

Introduction

Wiesenfeld *et al* (1985) introduced the concept of orofacial granulomatosis (OFG) to encompass, into a single entity, a group of conditions characterized by granulomatous inflammation in the oral and maxillofacial region. OFG is a specific clinical and pathologic entity, which may occur in an isolated form or in association with other systemic conditions, including Crohn's disease, Melkersson-Rosenthal syndrome and sarcoidosis.

As OFG has a number of possible aetiologies which are not distinguishable on the basis of the histological features (Patton *et al*, 1985; Wiesenfeld *et al*, 1985; James *et al*, 1986), it is very important to carry out a scrupulous diagnostic work-up including careful clinical, haematological and radiographic investigations. In the absence of a specific systemic condition such as Crohn's disease or sarcoidosis, the aetiology of OFG is still not clear and there is no evidence of a single causative agent (Challacombe, 1997). Various clinical features may be observed in orofacial granulomatosis with orofacial swelling being the most consistent component (Sciubba and Said-Al-Naief, 2003). Features include painless, non-pruritic, firm, asymmetrical, and occasionally unilateral oedematous swellings. Patients characteristically present with lip swelling that can be so severe as to cause facial disfigurement and lip swelling is a feature in over 90% of patients (Sanderson *et al*, 2005).

Labial oedema is usually accompanied by fissuring and purple discoloration. Although the swelling may be transient with complete resolution initially, repeated episodes of granulomatous inflammation may eventually lead to the formation of a firm indurated lip, secondary to fibrosis (Alexander and James, 1972). At the beginning, the lip enlargement can be unilateral, but it gradually becomes more symmetrical in nature (Nally, 1970; Vistnes and Kernahan, 1971; Alexander and James, 1972). Patients may present with swelling affecting only the upper or lower lip, but involvement of both lips is not uncommon. Gingivae, buccal mucosa, floor of the mouth and other sites in the oral cavity can also be involved (Hornstein, 1973; Worsaae *et al*, 1982; Levenson *et al*, 1984; Wiesenfeld *et al*, 1985; Mignogna *et al*, 2001).

To date, there is no generally accepted or preferred treatment for OFG. Some authors believe that the administration of systemic corticosteroids combined with topical analgesic preparations is the only satisfactory treatment mode (Neuhofer and Fritsch, 1984; Williams and Greenberg, 1991). Several other

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non-steroidal anti-inflammatory agents (clofazimine, dapsone, sulphapyridine, danazol, hydroxychloroquine and antibiotics) are reported to be useful in the management of OFG (Grove *et al*, 1977; Podmore and Burrows, 1986; Greene and Rogers, 1989; Van Zyl *et al*, 1991; Kano *et al*, 1992; Ochonisky *et al*, 1992; Sussman *et al*, 1992; Rogers, 1996). In patients who present with OFG as a manifestation of a hypersensitive reaction, the elimination of the allergen from the diet has been proved to be successful in leading to the resolution of the facial and lip swelling (Sweatman *et al*, 1986; Oliver *et al*, 1991; Lewis *et al*, 1995; Armstrong *et al*, 1997).

Patients with swollen lips because of OFG can experience morphological changes of the lips in relation to the activity of the disease and as a result of their treatment. The assessment of lip size is problematic for both the clinician and the patient as it is largely based on subjective perception and appraisal. There is therefore a need for a three-dimensional clinical record that enables precise measurement of the lips. To date, there is no published specific technique to objectively assess the size of the lips in OFG patients.

Previous methods reported have included nuclear magnetic resonance scanning, the use of a cheilometer and clinical photographs or reports of patient satisfaction. Nuclear magnetic resonance scanning (Sweatman *et al*, 1986) is capable of imaging soft tissues without using ionizing radiation but the high cost and its contraindication in certain patients make it unsuitable for routine use. Clinical photography has been the most commonly used technique (Rhodes and Stirling, 1965; Worsaae *et al*, 1982; Podmore and Burrows, 1986; Field and Tyldesley, 1989; Pachor *et al*, 1989; Zimmer *et al*, 1992; Kolokotronis *et al*, 1997; Girlich *et al*, 2002; Mignogna *et al*, 2003; Sciubba and Said-Al-Naief, 2003), but providing overall assessment in individual patients is essentially only semi-quantative and does not allow subtle changes to be detected. The use of a cheilometer has been attempted in our clinic (SJ Challacombe, unpubl. obs.) but was found not to be reproducible, especially in the more oedematous types of lip swelling. Patient satisfaction reporting can be a useful clinical outcome but very subjective, and not necessarily related to actual changes in the lip morphology.

The primary aim of this study was to suggest and evaluate an objective and reproducible method for assessing the lip measurement in OFG patients, appropriate for routine use and the assessment of changes in lip size in response to therapy. This study reports an evaluation of the use of lip impressions as (a) a more accurate method of measurement of lip swelling and its response to treatment and (b) the morphological labial changes in OFG patient in comparison with a group of healthy subjects.

Study subjects and methods

Subjects

The patients were enrolled from the Oral Medicine-Gastroenterology Clinic at Guy's Hospital (Guy's, King's and St Thomas Dental Institute, London) between October 2003 and June 2004. Twenty-one patients (11 males and 10 females) aged between 14 and 89 years (mean 35 years) took part in the study. They were all of Caucasian origin.

The study subjects were patients complaining of swollen lips and with established diagnosis of OFG made on the basis of clinical, haematological and histological investigations. Eight patients had a proven diagnosis of OFG associated with Crohn's disease. For 13 subjects, it was not possible to identify any systemic disorder associated with the swollen lips and they were therefore diagnosed as 'OFG alone'. The condition was oedema of both upper and lower lips in seven patients, 12 patients were complaining of swelling limited to the lower lip while two cases presented with enlargement of the upper lip only. For the patients with oedema of just one lip, either upper or lower, the non-involved lip was used as the control.

Thirteen of the 21 patients were put on a cinnamon- and benzoate-free diet as a single therapy, three patients were receiving both the exclusion diet and azathioprine, three patients were treated with azathioprine only and one patient was taking both azathioprine and mesalazine as he had an active intestinal Crohn's disease. One patient was treated with topical steroids.

Twenty-five healthy volunteers (10 males and 15 females) formed the control group. Seventeen were enrolled among the personnel of GKT Dental Institute and eight among the staff in a dental practice. They were all of Caucasian origin to match the patient group. The inclusion criteria for the healthy subjects comprised a medical history clear of any condition that could lead to labial oedema.

This study was independently reviewed and approved by the Guy's Research Ethics Committee (REC reference number 04/Q0704/2) and was undertaken with the understanding and written consent of each subject according to the World Medical Association Declaration of Helsinki.

Lip impressions

An impression of both upper and lower lips was taken for each study subject and the procedure was repeated during the follow-up. The follow-up period ranged from 1 to 37 months, with a mean of 11 months. Lip impressions from healthy subjects were used as the control. For nine of the healthy subjects, the impression was taken again after 3 months to evaluate normal variation in lip size with time.

The impressions were taken using a light-body addition-cured polyvinylsiloxane material (Coltène® President Plus Jet, Cuyahoga Falls, OH, USA). For people with moustaches or beards, a thin layer of vaseline was applied onto the hairs to prevent adherence to the impression material. Using the supplied dispenser, the light-body silicone material was squeezed on the lower vestibular sulcus (Figure 1a) and on the buccal and incisal edges of the lower teeth from canine to canine. The subjects were asked to bring their teeth together to reach a relaxed position of normal occlusion and the material was then applied on the upper vestibular sulcus

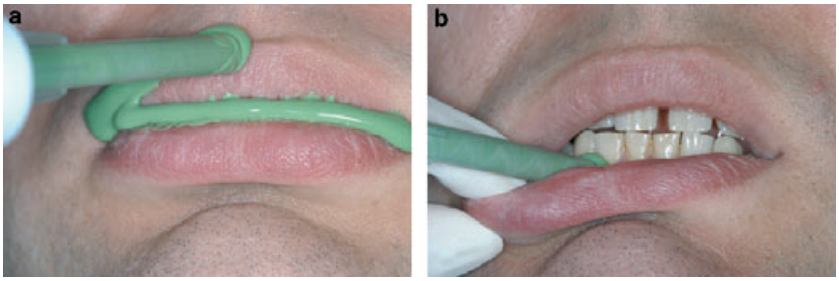

Figure 1 The light-body material is squeezed on the lower vestibular sulcus (**a**) and on the outer lips (**b**)

Figure 2 The final impression (**a**, **b**) and the model for measurements with callipers (**c**)

and on the buccal surfaces of the front teeth including the canines. The subjects were then invited to bring the lips together and the material was squeezed onto the outer lips in order to cover the whole vermilion border and part of the surrounding skin (Figure 2b). The whole procedure took about 1 min and a total of 5 min elapsed before the material was completely set. The subjects were asked to open gently to enable the impression to be detached intact. The removed impression was rinsed under cold running tap water and soaked in liquid disinfectant as per infection control regulations. Figure 2a, b shows the final lip impression. As taking lip impression has been a routine procedure in the Oral Medicine Department for the past 5 years, 27 of the impressions were already available from patients who had attended the Clinic before this study.

Plaster models

After applying a thin layer of surface-wetting agent (Wax-Mate, Bracon Dental Ltd, Etchingham, UK) on the impression material, models were cast using a medium-strength plaster (own brand provided by Bracon Dental Ltd). Two separate models were cast for upper and lower lips to avoid damage to the impression and to allow accurate measurements of the lips. The buccal surfaces of the front teeth were included in the models in order to have a visible inter-incisive line as a reference for the lip measurements.

Measurements

Callipers were used to measure the lips on the plaster models. The maximum diameter of the lips was measured at the midline (Figure 2c) and at one centimetre from the midline on both right and left sides. The measurements were recorded in millimetres.

Reproducibility of the method

To establish the inter-examiner reproducibility of the technique, two different impressions were taken from seven patients by two examiners during the same appointment. Twenty-four measurements of the cast model were repeated by the same examiner after 1 week to determine the intra-examiner reproducibility of the method.

Statistical analysis

The statistical analysis was carried out using the software packages Stata (StataCorp LP, TX, USA) and Excel (Microsoft Ltd, Reading, UK). An independent *t*-test was used to assess if there was any significant statistical difference in the size of lips between a normal population and OFG patients. A dependent *t*-test was used for assessing the follow up of patients and healthy volunteers.

Both the coefficient of variation and the Lin's concordance correlation coefficient were used to establish the inter-examiner reproducibility of taking lip impressions and the inter-examiner reproducibility of the measurements.

Results

Reproducibility of the method

The two series of 24 measurements carried out by the same examiner showed a coefficient of variation of 1.6%, while the Lin's concordance correlation coefficient was 0.99. The seven impressions that were taken twice by two different examiners showed a coefficient of

variation of 2.59%. Lin's concordance correlation coefficient was 0.97.

Healthy subjects
For the nine healthy volunteers for whom a second impression was taken after 3 months, a dependent *t*-test demonstrated no statistically significant difference between the first and second impressions in the measurements obtained from each site: upper midline, upper right, upper left, lower midline, lower right, lower left, suggesting that in a normal population the lips are stable in size over an established period of time. The independent *t*-test showed highly significant difference in lip size between healthy volunteers and OFG patients in all sites examined ($P < 0.0001$).

OFG patient follow up
In all 10 patients for whom impressions were taken before and after the commencement of the therapy, there was a significant decrease during a mean follow up of 11 months in all the sites: upper midline ($P < 0.002$), upper right ($P < 0.003$), upper left ($P < 0.001$), lower midline ($P < 0.002$), lower right ($P < 0.005$), lower left ($P < 0.05$). Eight of 11 patients whose impressions were taken after the initiation of the treatment showed a reduction during a mean follow up of 10 months on all sites ($P < 0.02$) apart from the lower right side ($P < 0.06$).

Discussion

This study reports a reproducible and accurate method for assessment of lip morphology and its response to treatment. The study was based on the observations that the assessment of treatment outcomes in OFG has been problematic and largely based on the subjective appraisal of both patient and clinician. Previous methods reported have included nuclear magnetic resonance scanning, the use of a cheilometer, the use of clinical photographs or reports of patient satisfaction. None of these methods has been acccepted as appropriate for objective routine clinical assessment. Patient satisfaction reporting can be a useful clinical outcome but very subjective, and not necessarily related to actual changes in the lip morphology. Sweatman *et al* (1986) reported the case of an OFG patient where changes in lip size were demonstrated using nuclear magnetic resonance scanning. This technique is capable of imaging soft tissues without using ionizing radiation but has many disadvantages, including the high cost and the contraindication for certain patients. In numerous case reports (Krutchkoff and James, 1978; Brook *et al*, 1983; Hernandez *et al*, 1986; Williams and Greenberg, 1991; Kano *et al*, 1992; Mignogna *et al*, 2001) and series of patients (Rhodes and Stirling, 1965; Worsaae *et al*, 1982; Podmore and Burrows, 1986; Field and Tyldesley, 1989; Pachor *et al*, 1989; Zimmer *et al*, 1992; Kolokotronis *et al*, 1997; Girlich *et al*, 2002; Mignogna *et al*, 2003; Sciubba and Said-Al-Naief, 2003) the swelling of the lips has been followed up and assessed using clinical photographs. The use of photographs offers the advantage of keeping a permanent record to monitor the progress of the disease but is essentially at best only semi-quantative and does not allow subtle changes to be detected. Consistency depends on using the same focal length, the same camera and film and the same conditions. Comparing different photographs of the same patient, therefore, is not sufficiently reliable for quantification of morphological changes of the lips. Thus to date it does not appear that an objective method to assess the morphological changes of the lips has been presented in the literature.

Direct measurements of lips size *in vivo* could present some limitations as lips are soft in texture and they can be easily distorted by even light movements as we found using a cheilometer. In addition, an *in vivo* technique does not result in a three-dimensional clinical record that could be used retrospectively for further measurements. We report in this manuscript a novel, reproducible and sensitive method for assessing lip measurement and changes in lip size in response to treatment in OFG.

A polyvinylsiloxane material was chosen for taking lip impressions as it is highly accurate, has a high dimensional stability after setting and has a very good biological compatibility. It presents with a very low viscosity and this characteristic allows the material to be dispensed onto patients' soft tissues, causing only minimal distortion.

Examiners who took the impressions found it easy to perform. For the reproducibility study, the order in which the impressions were taken was always the same: the first clinician was followed by the second after about 10 min. It is reasonable to assume that during this time the morphology of the lips did not change. Besides, as the distortion of the lips caused by the impression material was minimal, it was assumed that the impression obtained from the second examiner was not affected by the previous one. The technique appeared to be extremely reproducible and the two series of 24 measurements carried out by the same examiner showed a coefficient of variation of 1.6% (and Lin's concordance correlation coefficient of 0.99). The seven impressions that were taken twice by two different examiners showed a coefficient of variation of 2.59% and Lin's concordance correlation coefficient of 0.97. We believe that this level of reproducibility suggests that this technique can be used for the assessment of lip size.

Distortion of the morphology of the lips may occur if the patient is unable to relax the facial muscles. This can be overcome by trying to put the patients at ease and explaining the procedure step by step to ensure their compliance. In this study, no impression had to be repeated because of distortion or lack of patient cooperation.

Taking lip impressions has the advantage of providing plaster models that can be kept as permanent and stable clinical record and can be used to carry out measurements of patients' progress for future follow ups.

The major limitation of using callipers to measure the models of the lips is that it provides a one-dimensional measurement of a three-dimensional object. This could introduce bias when assessing the progress of the

disease. It could be assumed, for example, that a patient could present with morphological changes that may preferentially involve the vertical dimension of the lips compared with the diameter. However, clinical experience suggests that the labial oedema usually manifests with an increase in size which is proportional in all three dimensions. At the beginning of the disease, the lips could present with some degree of asymmetry, but it is unlikely that the oedema is distributed with such an irregular pattern to lead to a distortion that is manifest only in one direction, vertical, horizontal or lateral. However, to date, this assessment is based on clinical observation. It would be very useful to establish a method for the measurement of the lips that is able to quantify their three-dimensional changes. The technique presented here is novel and can be improved and adapted to different clinical situations.

In healthy subjects, a significant statistical difference was found for all sites established ($P < 0.01$). Patients with OFG were found to have significantly larger lips than the controls ($P < 0.0001$) which was as expected. In contrast to the OFG group, no significant changes in size were found in the healthy controls when they were reassessed after 3 months, suggesting that in the absence of disease there are no physiological changes in the dimensions of the lips over an established period of time. Thus all the morphological changes that were highlighted for the OFG group were due to either the disease activity or the response to treatment. An unexpected finding was a significant statistical difference between males and females in the controls for all the sites established ($P < 0.01$). This suggests that in a normal population males may present with lips that are larger in size compared with females. This difference was not noticed for OFG patients and the two groups of our study population were matched in terms of age and gender. It can be therefore postulated that labial oedema reflects only the activity of the disease and does not depend on the original size of the lips.

In both healthy subjects and OFG patients, the measurements showed that the lips were usually larger in the midline than laterally. This indicates that in our study population the swelling of the lips manifested with a proportional and regular oedema. This feature is in accordance with the characteristics of swelling of the lips reported in the literature. In OFG the labial oedema is often unilateral at the beginning, but gradually becomes more symmetrical in nature (Nally, 1970; Vistnes and Kernahan, 1971; Alexander and James, 1972). All our patients presented to the Oral Medicine Clinic at least 2 years after the onset of the disease. There are some patients in whom OFG does not manifest with swelling of the lips: in a recent study of 85 subjects, 89% showed labial oedema, suggesting that one in 10 have oral features of OFG other than lip swelling (Escudier *et al*, 2004). The technique of lip impressions would not be applicable to the minority of patients without lip lesions and further studies are needed to assess whether the response of lips to therapy reflects the disease activity in other sites of the oral cavity. Nevertheless, for OFG patients with apparent normal lips, taking a lip impression may be useful in detecting subclinical changes or in recording the initial stage of an unpredictable condition.

The follow up of OFG patients showed a significant improvement in their oral condition in relation to the therapy ($P < 0.001$). Three patients for whom the first impression was taken when they were already on the diet showed an increase in the size of the lower lip, suggesting that some patients are unresponsive to treatment. The findings suggest that the method should prove very useful in a more formal assessment of this and other therapies in OFG.

In conclusion, the results of the present study suggest that taking lip impressions is a simple and reliable technique for the routine evaluation and quantification of the size of lips and to monitor the response to therapy in OFG patients. It was also demonstrated that OFG patients can respond well to a cinnamon- and benzoate-free diet, as there was evidence that the lip size improved with this treatment.

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