Complications after permanent soft-tissue fillers

Kadouch, J.A.

2014

SUMMARY OF CHAPTERS

Treatment with injectable soft-tissue fillers, or 'fillers', has become an increasingly popular, minimally invasive alternative for facial rejuvenation and correction of certain medically indicated conditions. Such treatments require no anaesthesia or extensive preparation and are relatively easily performed in little time. In addition, they have an overall substantially low complication rate. However, the use of permanent fillers comes with higher complication rates and the term 'permanent' does not refer to the permanent result but to the permanent presence of the filling agent with the ensuing permanent risk of complications. Treatment of permanent filler complications are often burdensome for the patient and challenging for the treating physician due to the lasting character of the filler material and the difficulty to completely extract it.

The aim of the studies described in this thesis was to investigate and analyse permanent filler-associated complications. Doing so, we focused in particular on both intrinsic and extrinsic factors influencing the onset and type of these adverse events, as well as on possible diagnostic tools and treatment options for the different types of complications we have observed.

In Chapter 1 a general introduction is given on injectable soft-tissue fillers. Filler characteristics and treatment indications are discussed, as well as the historical background of filler materials.

Chapter 2 reviews the current treatment options for combination antiretroviral therapy (CART) induced facial lipoatrophy (FLA) in HIV-infected patients. FLA is the most common medical indication for treatment with soft-tissue fillers. CART reduces the morbidity and mortality in HIV-positive patients. One of the well-known side effects of this treatment is HIV-lipodystrophy syndrome (HIV-LS) and especially concurrent FLA. The early-generation nucleoside reverse-transcriptase inhibitors (NRTIs), thymidine NRTIs (tNRTIs) in particular, and the older protease inhibitors (PIs) have been strongly associated with the development of HIV-LS and FLA in HIV-infected patients. The atrophical facial changes in HIV-LS have a profoundly negative social and psychological impact on HIV-infected individuals: patients feel disfigured, stigmatized and isolated. In the last decade, many studies on the possible systemic treatment options for HIV-LS and local therapeutic options for FLA have been performed. Results suggest that systemic treatment with leptin, uridine, thiazolidinediones and growth hormone-releasing hormone may have a positive effect on both the metabolic abnormalities as well as the 'central' lipohypertophy, characteristic features of HIV-LS. However, to our knowledge no studies showing restoration of wasted facial subcutaneous adipose tissue after systemic therapies have been published. At present, local invasive treatments such as injections with soft-tissue fillers seem most promising. Soft-tissue fillers are a relatively simple and efficient treatment option for FLA. Especially, the biodegradable semi-permanent fillers combine a good effect with durability and an acceptable safety profile. Lipofilling, using autologous adipose tissue, has recently also

shown promising results. The best way to prevent or restrict the development of FLA remains the exclusion of tNRTIs from the CART schedule.

Chapters 3 to 6 focus on different aspects of permanent filler-related delayed-onset complications. From 2005 to 2011 a total of 85 patients were referred to our outpatient clinic with delayed-onset complications, starting 2 weeks after injections of permanent filling agents in the face. In **Chapter 3** we evaluate the factors influencing the onset and type of these adverse events. The used fillers in our cohort (40 males, 45 females; mean age 54, range 27-79) were polyalkylimide gel (PAIG), hydroxyethylmethacrylate/ethylmethacrylate (HEMA/EMA), polymethylmethacrylate (PMMA) polyacrylamide hydrogel (PAAG) and liquid injectable silicone (LIS). The majority of the 85 patients underwent soft-tissue augmentation for facial rejuvenation (n = 51, 60%), whereas 40% (n = 34) were HIV-positive patients treated for CART-induced FLA. The complications observed in this study could be categorized into noninflammatory nodules, low-grade inflammations, abscesses, and migrations of filler deposits. Filler-abscesses occurred only after injection with PAIG and were significantly more frequent in HIV-positive patients (p = .001). Lag times until onset and type of delayed-onset complication varied per filler material. Thus, the intrinsic characteristics of the injected filler and the immune status of the patient appear to be important factors in time of onset and type of delayed-onset complication observed. In addition, 24 of the 85 patients (28%) had undergone a facial or oral (dentist of dental hygienist) invasive procedure before the occurrence of a complication. The exact mechanisms responsible for provoking complications after invasive procedures in the vicinity of existing filler deposit remains to be elucidated. The possibility of a secondary bacterial contamination of a filler deposit during such an invasive treatment poses a problem for the use of permanent fillers. Aging and CART-induced FLA are dynamic, on-going processes that will need 'touch ups'. Additional injections at the site or in the direct vicinity of an existing permanent filler deposit will always involve the risk of infection. In this chapter we propose a treatment strategy for delayed-onset facial complications after permanent filler injections based on our clinical experience.

Filler-related complications also occur on other sites of the human body. Numerous studies have described complications after injections of permanent fillers in the breasts or buttocks. In **Chapter 4** we describe six patients referred to our outpatient clinic with complications of penis and/or scrotum enlargement after injections with permanent soft-tissue fillers. The injections were performed in Dutch, Belgian, Turkish and American private clinics. The encountered permanent fillers were LIS, PAIG and PAAG. The observed complications varied from swelling and nodules, to low-grade infections and persisting skin defects. In five patients surgical treatment was mandatory. Three patients required repetitive surgery. The results of these procedures were all cosmetically disappointing. In a review of the literature no publications on penile girth augmentation with PAIG or PAAG were found. The majority of the 14 papers we found on the use of LIS for penile girth augmentation state that its use may lead to

serious complications. Remarkably, we learned that, at the time of submission of this manuscript, several private clinics in the Netherlands and in Belgium were still using PAAG as permanent filler for penile girth enhancement.

While the mainstay of diagnosis of filler-related complications should always be a careful history and clinical examination, we have experienced that it can be difficult to determine the nature and extent of certain complications in clinical practice. In such cases an investigative imaging tool to aid in the assessment of filler-related complications could be helpful. Previous studies have reported on various imaging techniques that have been used for analysis of injected filler material, such as ultrasound, magnetic resonance imaging (MRI) and computed tomography scan. In **Chapter 5** we analyze the value of MRI in a cohort of 32 patients (16 male, 16 female; mean age 55, range 25-76 years) with delayed-onset complications after facial injections with permanent fillers (PAIG *n* = 30, PAAG *n* = 2, HEMA/EMA *n* = 2). In total 107 site-specific evaluations of the correlation between clinical and radiological findings were performed. With regard to the localization of the filler deposits, a strong agreement of 83% was observed between clinical assessments and MRI (89 of 107). For the observed complications the overall clinicoradiologic agreement was assessed as substantial (70 of 107, 65%). In particular migration of filler material appeared to be difficult to determine clinically, compared to detection of filler migrations with MRI (clinicoradiologic agreement of 9%). In addition, we observed that migration is frequent in deposits with concurrent inflammation (5 of 11, 45%) or abscess (9 of 18, 50%). In the subgroups with a clinically assessed LGI (*n* = 14) or abscess (*n* = 14) treatment strategy was modified according to MRI results in 25% of cases (7 of 28). Our results suggest that MRI may be a useful pre-treatment diagnostic tool and aid in therapeutic decision-making for patients with inflammatory complications from permanent fillers that possess a certain 'migratory potential' (*i.e.* non-absorbable hydrogel polymers like PAIG and PAAG). In addition, possible indications for the use of MRI in the management of permanent filler complications are defined in this article.

Granulomatous foreign-body reactions (GFBRs) are often implicated as type of filler-complication. This kind of reaction can only be established by histologic examination. Clinically however, they usually have the appearance of lumps and bumps lacking features of inflammation (*rubor, calor, dolor*). The exact pathogenesis of filler-induced GFBRs, or 'filler granulomas', has yet to be elucidated. Several authors have compared filler granulomas to the 'naked' granulomas seen in sarcoidosis. Since plasmacytoid dendritic cells (pDCs) are the main source of type I interferon α (IFN-α) in man and systemic IFN-α therapy can cause late-onset sarcoidal GFBRs in patients injected with permanent fillers, we hypothesized that IFN-α producing pDCs are present in 'spontaneous' GFBRs to permanent filler agents. In **Chapter 6** we investigate this hypothetical role of pDCs. To detect pDCs we stained skin biopsies from 19 patients with late-onset GFBRs to PAIG, PAAG, HEMA/EMA or LIS with monoclonal antibodies to CD123 (interleukin-3 receptor α-chain), which is strongly expressed on pDCs.

Immunostaining with anti-CD11c, positive on myeloid DCs (mDCs) and histiocytes, was performed for comparison. The histologic features of the filler deposits and the observed GFBRs were in agreement with previous reports, but grading of the inflammatory infiltrates observed histologically did not correlate with clinical features of inflammation. Immunostaining for CD123 did not detect pDCs in 8 of 10 PAIG-, 1 of 2 PAAG- and the 5 LIS biopsies. In contrast, all 4 HEMA/EMA biopsies contained collections of pDCs in lymphocytic infiltrates close to filler particles and adjacent sarcoidal granulomas. All histiocytes and giant cells present in GFBRs to the different fillers showed high expression of CD11c, impeding recognition of CD11c+ mDCs. Our data suggest that pDCs are not important in GFBRs to the permanent soft-tissue fillers PAIG, PAAG and LIS, but may contribute to the severe sarcoidal granulomas associated with injected HEMA/EMA. Recruited pDCs may exert their pro-inflammatory effects by release of IFN-α at the site of these filler deposits.

In Chapter 7 we revert to the subgroup of HIV-positive patients suffering from FLA. Numerous studies have shown that FLA treatment with facial injections of soft-tissue fillers effectively improves quality of life (QoL) and lowers depression rates. Due to the higher complication rates associated with permanent fillers, treatment with semi-permanent fillers such as poly-L-lactid acid (PLLA), calcium hydroxylapatite (CaHA) and 'modified' (*i.e.* cross-linked or high-density) hyaluronic acid (HA) currently generates the most promising outcomes. PLLA and CaHA differ in respect to HA in the sense that they have a biostimulatory effect and induce the production of neocollagen. In this prospective study we enrolled 82 HIV-positive patients suffering from FLA (77 male, 5 female; mean age 51, range 31-72 years) for treatment with PLLA or CaHA in order to analyze the association between the measured treatment effects on MRI and changes in QoL. Significant increases in total subcutaneous thickness (TST) of the injected regions could be identified on MRI in nearly all patients at one year post-treatment. This increase in thickness was formed by well-demarcated, pleomorphic, hypointense subcutaneous tissue, which we designated as neocollagen. Mental health and social functioning improved and depressive symptoms decreased after treatment. Improvement of QoL seems to be positively associated with the filler-induced increase in TST. Furthermore, this study also shows that MRI can quantify FLA treatment effects of PLLA and CaHA.

In Chapter 8 the main findings of this thesis are discussed and related to future perspectives on the diagnosis and treatment of permanent filler complications. In addition, the anticipated developments in the world of soft-tissue fillers in general are reviewed.