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Review Article

Revolution In Medical Aesthetics: The Role Of Lipofilling And Advanced Cellular Therapies.

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Abstract

Lipofilling , or facial fat grafting with autologous fat, has been widely used in aesthetic and reconstructive medicine due to its biocompatibility and regenerative potential. The technique, which consists of collecting, processing and reinjecting the patient's own fat, has evolved significantly in recent decades. However, challenges such as unpredictable graft reabsorption and variability in results still represent barriers to its wider application.

This review critically analyzes recent advances in lipofilling , addressing best practices to maximize cell viability and graft longevity. Topics discussed include differences in harvesting methods (syringe-assisted suction vs. traditional liposuction), the influence of donor sites on graft quality, and purification techniques such as decantation, centrifugation, and filtration. In addition, the impact of adipose graft processing on cell survival is explored, emphasizing the importance of preserving the cellular microenvironment to optimize vascularization and tissue integration.

Comparing lipofilling with emerging regenerative therapies, such as polydeoxyribonucleotide (PDRN) and exosomes , it is observed that these technologies can significantly enhance the effects of adipose grafting. Recent studies demonstrate that the combination of lipofilling with cellular biostimulators improves graft survival, reduces inflammation and promotes tissue regeneration, suggesting that these combined treatments can redefine the therapeutic standards of aesthetic medicine. The increasing incorporation of exosomes derived from mesenchymal stem cells and specific growth factors has shown promising results in maintaining graft quality and improving skin homeostasis.

Although technological advances have allowed greater predictability in results, limitations still persist, such as the need for multiple sessions to achieve satisfactory volume and the difficulty in standardizing protocols to optimize the technique. Prospective studies and more robust clinical trials are needed to consolidate clinical guidelines and fully understand the mechanisms underlying the interaction between fat grafts and the recipient environment.

In conclusion, lipofilling continues to play a central role in aesthetic medicine, with applications that go beyond volumization , encompassing tissue regeneration and biostimulation. The synergy between lipofilling and new therapeutic approaches, such as PDRN and exosomes , represents a promising milestone for the future of regenerative therapies, revolutionizing the way we address skin aging and facial volumetric restoration.

INTRODUCTION

Lipofilling , also called facial fat grafting with autologous fat, has emerged as a central technique in aesthetic and regenerative medicine, being widely used for volumetric restoration, skin rejuvenation and improvement of tissue quality (Nemir et al ., 2021). Since its first description in the 19th century, the technique has evolved significantly, driven by advances in adipose tissue harvesting, processing and injection methodologies, aiming to maximize cell survival and tissue integration (Jurgens et al., 2008; Rohrich et al., 2004). However, variability in clinical results, graft resorption rate and the need for standardization of protocols remain important challenges (Nemir et al., 2021).

Lipofilling involves the extraction of fat from donor sites via liposuction, followed by processing and reinjection into the recipient site (Di Taranto et al., 2015). Although this approach offers significant advantages, such as biocompatibility and abundant availability of adipose tissue, the graft survival rate is still unpredictable, ranging from 30% to 80%, depending on the techniques employed (Padoin et al., 2008). Studies suggest that factors such as donor site choice, graft purification method, and injection technique play crucial roles in cell viability and outcome longevity (Schipper et al., 2008; Small et al., 2014).

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In recent years, emerging regenerative therapies, such as polydeoxyribonucleotide (PDRN) and exosomes , have been investigated as potential adjuvants to improve lipofilling outcomes (Kim et al., 2009; Canizares et al., 2017). PDRN acts as a cellular biostimulator , promoting angiogenesis and tissue regeneration, while mesenchymal stem cell-derived exosomes contain growth factors and messenger RNA that enhance cell differentiation and inflammatory modulation (Francis et al., 2019; Girard et al., 2013). These innovative approaches have demonstrated significant benefits in reducing graft resorption and improving tissue quality.

Despite progress, challenges remain regarding the standardization of fat processing techniques. Methods such as centrifugation, decantation, and filtration are frequently employed, but there is disagreement regarding the impact of these techniques on fat cell viability and graft retention (Conde-Green et al., 2010; Xie et al., 2010). Furthermore, the recipient site environment, including pre-existing vascularization and inflammatory response, directly influences grafting success, suggesting that combined approaches may be more effective (Khouri et al., 2014).

This review article aims to critically analyze recent advances in lipofilling , discussing its indications, advantages and limitations, as well as the integration of new regenerative therapies in the optimization of this technique. Through the review of the main published studies, we aim to provide a comprehensive overview of the impact of lipofilling on modern aesthetic medicine and the future perspectives for improving this approach.

HISTORY AND EVOLUTION OF THE TECHNIQUE

grafting has its origins dating back to the late 19th century, when the first reports of fat grafting were documented. However, only in recent decades has the technique evolved into a widely accepted procedure in aesthetic and regenerative medicine. The first documented attempt at autologous fat grafting occurred in 1893, when the German surgeon Gustav Neuber used adipose tissue to correct a facial depression in a patient with osteomyelitis (Neuber , 1893). Although pioneering, his work was not widely accepted at the time due to early graft resorption. In the following decades, several surgeons attempted to use autologous fat for tissue reconstruction, but inconsistent results limited its clinical application. In 1950, Peer demonstrated that approximately 50% of transplanted adipose cells would not survive the procedure, which reinforced the need for new approaches to increase graft viability (Peer , 1950).

A major breakthrough occurred in the 1980s with the popularization of liposuction, a technique that allowed for more delicate and voluminous fat extraction, opening up new possibilities for its reinjection. Illouz (1983) was one of the pioneers in describing liposuction as an efficient method of fat harvesting while preserving cell viability (Illouz , 1983). Fournier (1985) subsequently improved the technique by introducing syringe liposuction, which minimized trauma and improved fat cell survival (Fournier, 1985). During the 1990s, lipofilling began to gain ground in aesthetic and reconstructive medicine. Coleman (1997) developed a refined fat grafting protocol , known as the Coleman technique, which emphasized centrifugation of fat prior to reinjection, removing impurities and promoting a more stable graft (Coleman, 1997). His technique revolutionized the modern approach to fat grafting , becoming a gold standard used to this day. He achieved the feat of obtaining more than 80% graft survival, due to fat processing.

With the growing demand for less invasive and more natural-looking aesthetic procedures, the last decade has seen significant advances in lipofilling . Studies have shown that the fat donor site influences the amount of mesenchymal stem cells present, impacting graft survival rate (Padoin et al., 2008; Jurgens et al., 2008). Furthermore, research suggests that graft viability can be improved with purification methods that avoid excessive exposure to the environment and optimize the presence of regenerative cells (Rohrich et al., 2004; Schipper et al., 2008). Another important advance has been the introduction of regenerative therapies to improve adipose graft integration. The use of polydeoxyribonucleotide (PDRN), a biostimulant derived from salmon DNA, has demonstrated angiogenic potential , reducing inflammation and promoting tissue regeneration when combined with lipofilling (Kim et al., 2009). Furthermore, mesenchymal stem cell-derived exosomes have been investigated as agents to improve grafted fat retention and stimulate cell regeneration (Francis et al., 2019; Girard et al., 2013).

In recent years, the fragmentation of autologous fat has led to the development of new approaches in fat grafting , giving rise to the Microfat and Nanofat techniques . Unlike traditional grafting, these techniques aim to reduce the size of fat particles and optimize their regenerative properties. Microfat consists of mechanical processing of fat to reduce its diameter, maintaining the presence of adipocytes and mesenchymal stem cells. This type of fat is used for volumetric filling of delicate regions, such as the face and hands, ensuring better tissue integration and lower risk of reabsorption (Tonnard et al., 2013). Nanofat represents an even more advanced stage of fat purification; in this fraction, we do not find viable adipocytes, but only multipotent stem cells. The technique involves the emulsification and filtration of adipose tissue until a liquid rich in adipose tissue-derived stem cells (ADSCs), growth factors and extracellular matrix, but without viable adipocytes, is obtained. Nanofat is not used for volumization , but rather for skin regeneration, being employed in the treatment of fine wrinkles, dark circles and atrophic scars,

improving skin quality (Tonnard et al., 2013; Tremolada et al., 2016). Recent studies indicate that Nanofat can act as a potent biostimulator , inducing angiogenesis and dermal regeneration, and can be combined with therapies such as PDRN and exosomes to enhance their effects (Tremolada et al., 2016). The clinical impact of these techniques is expanding the applications of lipofilling beyond volumization , making it a key tool in regenerative medicine and tissue rejuvenation.

Currently, the use of closed fat processing systems has been studied as an alternative to avoid contamination and improve cell viability (Nemir et al., 2021). Studies also investigate the impact of combining lipofilling with bioengineering techniques, such as the use of biocompatible scaffolds for three-dimensional support and more efficient vascular integration (Canizares et al., 2017). Given these advances, lipofilling is no longer limited to volumetric replacement, but also plays a fundamental role in regenerative medicine, promoting tissue repair and improving skin quality. The continued development of improved techniques and the incorporation of new biostimulatory therapies promise to further transform this field, making lipofilling an essential tool for the future of medical aesthetics and tissue regeneration.

MAIN CONCEPTS AND DEFINITIONS

Autologous fat grafting (AFG) refers to the transplantation of adipose tissue without direct vascularization, being one of the most widely used methods for volumetric filling, improvement of skin texture and tissue biostimulation (Nemir et al., 2021; Jurgens et al., 2008). The procedure can be divided into three main stages: fat collection, performed by liposuction from donor areas such as the abdomen, flanks or thighs, using syringes or mechanical suction systems (Rohrich et al., 2004); graft processing, in which the adipose tissue is subjected to methods such as centrifugation, decantation or filtration to remove residual fluids and preserve viable adipocytes (Schipper et al., 2008); and injection into the recipient site, where the processed fat is applied in multiple tissue planes to maximize vascularization and avoid graft necrosis (Coleman, 1997).

The retention rate of grafted fat varies between 30% and 80%, depending on factors such as harvesting method, processing, vascularization of the recipient tissue and the presence of biochemical stimuli that favor angiogenesis and cell differentiation (Padoin et al., 2008). The main factors that affect graft viability include the fat donor site, since studies suggest that the concentration of mesenchymal stem cells varies according to the donor region. Areas such as the abdomen and medial aspect of the thigh have a higher density of these cells, influencing graft retention (Rohrich et al., 2004). The processing technique also plays a critical role, since methods such as decantation preserve a greater number of viable adipocytes, while centrifugation can compromise cellular integrity at high speeds (Schipper et al., 2008). Furthermore, the injection technique affects graft survival, since the deposition of fat in small tunnels improves vascularization, reducing graft necrosis and promoting greater predictability in results (Small et al., 2014).

In recent years, lipofilling has been combined with regenerative therapies to enhance its effects and improve graft retention. Among the most promising approaches are polydeoxyribonucleotide (PDRN), a biostimulator derived from salmon DNA, which promotes angiogenesis and tissue regeneration, reducing inflammation and optimizing adipose graft retention (Kim et al., 2009), and exosomes derived from mesenchymal stem cells, which are extracellular vesicles containing growth factors and messenger RNA, modulating the inflammatory response and favoring cell differentiation, contributing to adipose graft survival and skin regeneration (Francis et al., 2019).

LIPOFILLING STUDIES

The scientific literature on lipofilling encompasses a diversity of methodological approaches to assess the viability of the technique, its clinical efficacy and the impacts of different variations of the procedure. The main methods employed can be categorized into in vitro studies, preclinical studies (animal models), clinical trials and systematic reviews. In vitro studies are widely used to investigate cell viability, differentiation of adipose tissue-derived mesenchymal stem cells (ADSCs) and the effects of fat processing on cell integrity. Among the main methods employed, trypan blue exclusion tests , MTT assay and flow cytometry were commonly applied to assess adipocyte viability and proliferation after different methods of adipose graft harvesting and processing (Schipper et al., 2008; Conde-Green et al., 2010). Comparisons between decantation, centrifugation, and filtration have been performed to determine which method best preserves cell viability and reduces the amount of unwanted debris in the adipose graft (Xie et al., 2010). Furthermore, some studies have evaluated the effect of different concentrations of local anesthetics, such as lidocaine and epinephrine, on cell viability and ADSC proliferation (Kim et al., 2009; Francis et al., 2019).

Animal models are frequently employed to investigate adipose graft retention, vascularization effects, and inflammatory response. Among the main experiments, studies performed fat grafting in immunocompromised rats and mice, where processed adipose tissue was grafted subcutaneously into these animals, and the graft retention rate was assessed by weighing, histology, and computed tomography imaging (Padoin et al., 2008 ; Nemir et al., 2021). Graft retention was also assessed by histological stains, such as hematoxylin-eosin and Oil Red O, in addition to immunohistochemistry

to detect the presence of angiogenesis and inflammation at the graft site (Rohrich et al., 2004). Other studies have analyzed the influence of vascularization on the graft retention rate, evaluating whether grafted fat retains better in well-vascularized tissues, such as muscle, compared to less irrigated areas, using angiography and electron microscopy techniques (Karacaoglu et al., 2005; Shi et al., 2016).

Clinical studies represent a significant part of the literature on lipofilling and focus on its safety, efficacy and patient satisfaction. Randomized clinical trials have compared the graft retention rate using different techniques, such as Microfat and Nanofat , evaluating the results by ultrasonography, magnetic resonance imaging and 3D volumetry (Di Taranto et al., 2015; Small et al., 2014). Some studies have investigated the impact of the use of PDRN, exosomes and PRP (platelet-rich plasma) on the retention rate of grafted fat, with clinical and histological evaluations (Canizares et al., 2017). In addition, patient satisfaction was assessed through subjective scales, such as the Global Assessment of Facial Aesthetics Scale (GAIS), and standardized questionnaires on quality of life (Khouri et al., 2014).

Several studies have systematically reviewed the literature on lipofilling , consolidating data from clinical and preclinical trials. Systematic reviews have identified key elements that impact grafted fat survival, including harvesting technique, purification, injection, and recipient tissue factors (Conde-Green et al., 2010; Xie et al., 2010). Meta-analyses have evaluated the efficacy of different approaches, such as centrifugation versus decantation, or Nanofat versus adjuvant PRP, consolidating data from multiple clinical trials (Schipper et al., 2008). In addition, reviews have addressed the incidence of complications, such as fat necrosis, contour irregularities, and partial graft resorption, analyzing retrospective data from large clinical case series (Khouri et al., 2014).

Lipofilling research uses a multidisciplinary approach, combining in vitro studies, animal models, clinical trials and systematic reviews to improve the technique and optimize its results. The main aspects investigated include the methods of processing the adipose graft and their impact on cell viability, regenerative therapies associated with lipofilling to improve the graft retention rate and long-term clinical studies to evaluate the aesthetic and functional efficacy of the technique.

TRENDS AND FUTURE DIRECTIONS IN LIPOFILLING

Based on the review of the most recent articles on lipofilling and associated regenerative therapies, some trends and future directions can be identified. The literature points to a growing interest in new approaches to optimize the technique, reduce adipose graft resorption, and expand its applications in aesthetic and regenerative medicine. One of the main challenges of lipofilling remains adipose cell survival, and researchers have explored several approaches to increase cell viability and reduce graft resorption. Graft enrichment with adipose tissue-derived stem cells (ADSCs) has been studied as a strategy to improve grafted fat retention and promote better integration with the recipient tissue (Nemir et al., 2021). Furthermore, the use of growth factors and biomolecules, such as ADSC- derived exosomes and PRP (platelet-rich plasma), has shown potential to improve vascularization and reduce grafted fat resorption (Francis et al., 2019). Another aspect under development is the standardization of adipose tissue processing methods. Comparisons between decantation, low-speed centrifugation and filtration indicate that less aggressive methods better preserve cell viability (Conde-Green et al., 2010).

In recent years, regenerative approaches have been studied as potential adjuvants to lipofilling to optimize graft retention and enhance its functionality. Exosomes derived from mesenchymal stem cells are being investigated for their ability to modulate the inflammatory response and promote angiogenesis, which favors tissue regeneration and improves graft retention (Kim et al., 2009). Polydeoxyribonucleotide (PDRN) has demonstrated potential to stimulate cell proliferation and angiogenesis, being a promising approach to improve adipose graft integration and reduce postoperative fibrosis (Canizares et al., 2017). Furthermore, lipofilling variants , such as Nanofat and Microfat , demonstrate a significant biostimulatory effect , being applied to improve skin texture and regeneration of damaged tissues, with less focus on volumization (Tonnard et al., 2013).

Advances in processing and injection technologies have also been an important focus to improve the clinical outcomes of lipofilling . Automated equipment that avoids exposing adipose tissue to the external environment is being developed to minimize contamination and optimize cell viability (Hanson et al., 2019). In addition, artificial intelligence (AI) has been studied to analyze 3D images and assist in more homogeneous distribution of the graft, reducing post-procedure irregularities (Shi et al., 2016). Another recent innovation is ultrasound-guided lipofilling , which has been tested in clinical trials and can improve the accuracy of the technique, reducing complications, especially in difficult-to-access areas (Karacaoglu et al., 2005).

Although research on lipofilling has advanced significantly, there are still important gaps in knowledge that should be addressed in future studies. The rate of fat resorption remains a difficult variable to predict, and there is no definitive consensus on which methods ensure the greatest graft retention (Di Taranto et al., 2015). Furthermore, the impact of the donor site on graft viability is not yet fully understood, as different regions of the body have variable concentrations of stem cells and may influence graft quality,

requiring further investigation to establish an ideal standard (Padoin et al., 2008). The impact of biomolecules, such as exosomes , PRP, and PDRN, is not yet fully understood at the molecular level, and further studies are needed to determine the optimal dosage and frequency of application (Girard et al., 2013). Lipofilling is also being explored for applications in unconventional areas, such as scar treatment, burn tissue regeneration, and neuromuscular injury repair, but more clinical trials are needed to prove its efficacy in these scenarios (Khouri et al., 2014). Furthermore, the long-term safety of lipofilling is not yet fully established, as some late complications, such as calcifications and fat necrosis, have been reported, and there are still few studies with follow-up longer than 10 years (Xie et al., 2010).

The future of lipofilling is being shaped by technological advances, integration with regenerative therapies, and efforts to standardize techniques and protocols. Future research should explore new strategies to increase graft retention, reduce complications, and expand its applications to different areas of regenerative medicine. The growing interest in graft biostimulation with exosomes and PRP, together with the development of minimally invasive techniques guided by AI and ultrasound, promises to revolutionize the field of aesthetic and regenerative medicine, making lipofilling an increasingly sophisticated and effective therapeutic option.

CRITICISMS AND LIMITATIONS OF EXISTING STUDIES ON LIPOFILLING

Despite significant advances in lipofilling research , the literature still presents several methodological limitations and knowledge gaps. One of the main limitations of lipofilling studies is the wide variability in the methods used for harvesting, processing, and injection of grafted fat. This heterogeneity makes it difficult to compare studies and prevents the definition of an ideal protocol to maximize adipose graft retention (Nemir et al., 2021). Different harvesting techniques are used, including syringe liposuction and pump-assisted liposuction, which apply different suction pressures and can influence cell viability and graft outcomes (Schipper et al., 2008). Furthermore, there is no consensus on which adipose tissue processing method best preserves cell viability. Some studies indicate that high-speed centrifugation may impair adipose cell viability, while decantation or mechanical filtration preserve more stem cells (Xie et al., 2010). The injection technique is also a determining factor, as the volume injected per pass and the dispersion of the graft in the recipient tissue impact graft retention, but there is no standardization among clinical trials (Small et al., 2014).

Another important limitation is the lack of long-term studies and adequate clinical follow-up. Adipose graft resorption occurs over months or years, but few studies follow patients for periods longer than 12 months (Padoin et al., 2008). In addition, there is a lack of clinical data on late effects, such as fibrosis, calcifications or contour irregularities (Khouri et al., 2014). Some studies suggest that lipofilling may be influenced by patient metabolic variations, such as changes in body weight and aging, but these factors are rarely controlled in clinical trials (Di Taranto et al., 2015).

The fat harvesting site may influence graft quality, but studies have not yet reached a consensus on which body region provides better results. Some studies suggest that fat from the abdomen and medial thigh contains a higher concentration of stem cells, favoring graft retention (Rohrich et al., 2004). However, other studies indicate that there are no significant differences between donor sites and that the choice should be based on the availability of adipose tissue and the surgeon's preference (Jurgens et al., 2008). The lack of randomized controlled comparative studies makes it difficult to obtain conclusive evidence.

Standardized assessment of graft survival rate also represents a significant limitation. Most lipofilling studies evaluate results subjectively, with qualitative methods or imprecise volumetric analyses. Objective methods, such as magnetic resonance imaging (MRI), three-dimensional ultrasound, and computed tomography (CT), are rarely used in clinical trials to quantify fat graft retention (Canizares et al., 2017). Some studies use histological and immunohistochemical assessments, but variability between protocols limits comparability between studies (Francis et al., 2019). Furthermore, most clinical studies do not take into account individual patient factors, such as age, metabolism, and genetic factors, which may impact graft retention.

The lack of evidence on regenerative therapies associated with lipofilling is also a relevant issue. The use of exosomes , PDRN and PRP as adjuvants to lipofilling has shown promising results, but the exact mechanisms of action are not yet fully understood. Studies determining the ideal dosage and frequency of application of these therapies to enhance graft retention are lacking (Kim et al., 2009). Some studies indicate that the combination of PRP and lipofilling can reduce the resorption rate, but the results are inconsistent among clinical studies (Girard et al., 2013). Exosomes derived from mesenchymal stem cells are a promising innovation, but there are few randomized controlled clinical trials proving their long-term efficacy and safety (Nemir et al., 2021).

Although considered a safe procedure, lipofilling is not without risks, and some complications still need to be further studied. Irregular graft resorption can lead to the formation of hardened areas or calcifications, resulting in fat necrosis and the formation of oily cysts (Xie et al., 2010). Furthermore, lipofilling is widely used in breast reconstruction, but there is still debate about whether it can interfere with the visualization of mammographic lesions , potentially hindering

the early diagnosis of breast cancer (Khouri et al., 2014). Another rare but serious complication is fat embolism, which can occur when injected fat inadvertently enters the bloodstream, reinforcing the need for standardization of application techniques (Nemir et al., 2021).

lipofilling research still faces methodological challenges and knowledge gaps. The lack of standardization in graft harvesting, processing, and injection methods, combined with the absence of long-term studies, makes it difficult to reach a consensus on best practices. Going forward, it is essential that lipofilling studies standardize clinical protocols to allow for more reliable comparisons, extend patient follow-up to assess long-term graft retention, and better explore the effects of associated regenerative therapies, such as PRP, exosomes , and PDRN. In addition, the use of objective assessment methods, such as magnetic resonance imaging and computed tomography, is essential to quantify graft retention rates. With these advances, it will be possible to consolidate lipofilling as a more predictable, safe, and effective technique in aesthetic and regenerative medicine.

CONCLUSION

Lipofilling has established itself as a fundamental technique in aesthetic and regenerative medicine, evolving from a procedure exclusively focused on volumetric replacement to a multifunctional approach with biostimulatory and regenerative potential. Advances in donor site selection, adipose tissue harvesting and processing methods , and injection techniques have contributed significantly to improving graft retention, although challenges such as unpredictable fat reabsorption and variability in results still persist.

The development of regenerative technologies, such as polydeoxyribonucleotide (PDRN), exosomes and platelet-rich plasma (PRP), has shown promising results in inflammatory modulation, angiogenesis and optimization of adipose graft cell viability. The combination of these strategies with conventional lipofilling may represent a new paradigm in regenerative medicine, allowing not only greater predictability in results, but also expanding the indications of the procedure to areas such as tissue rejuvenation, healing and repair of damaged tissues.

However, the current literature still presents significant gaps, mainly related to the lack of standardization of clinical protocols, heterogeneity in fat processing methods, and the absence of long-term studies evaluating the safety and durability of results. The need for randomized clinical trials with greater methodological rigor is essential to consolidate evidence-based guidelines and improve the reliability of the technique.

In light of this, the future of lipofilling looks promising, driven by technological innovations such as artificial intelligence applied to predicting results, the use of ultrasound guides for greater precision in grafting, and the development of closed fat processing systems. The continued evolution of the technique and the integration of new regenerative therapies may not only revolutionize aesthetic treatments, but also expand the clinical applications of lipofilling to medical areas that are still little explored. Thus, the search for more effective protocols and the investigation of the interactions between fat grafts and the tissue microenvironment will be fundamental to consolidate this approach as an essential pillar of modern regenerative medicine

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Conflict of interest

The authors confirm that they have no conflicts of interest in relation to this work.

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