The Regenerative Clinic

Lipogems® – A Miniature Literature Review

Evidence and outcomes

Lipogems®
A Miniature Literature Review

1. What the research shows

Regenerative medicine is an interdisciplinary field that seeks to develop the science and tools that can help repair or replace damaged or diseased human cells or tissues to restore normal function.

It holds the promise of revolutionising the treatment of many conditions in the 21st century.

In 2001, Zuk, et al. [1] were one of the first to report that lipoaspirates ("junk" fat removed during liposuction) are in fact a useful reservoir of multipotent adult progenitor cells.

The Power of Fat

Fat, also referred to as adipose tissue, has been used for decades to treat slow healing and difficult wounds as well as many other conditions [2].

Recently there have been advances in understanding the composition of the abundant variety of cells within our fat. We are now able to separate the different cell types including mature adipocytes, haematopoietic cells, endothelial cells, pericytes, and adipose stem cells. These cells have important restorative and healing properties which are conveyed through a huge number of compounds which have anti-inflammatory and regenerative properties.

There is a steady growth in the number of scientific studies looking at ways to utilise fat cells to treat musculoskeletal conditions. However, it is in the last decade that significant progress in the medical uses for fat have occurred. One of the devices that has been used the longest and has been assessed in a number of scientific studies is the Lipogems® system. This device has been available since 2013 and has FDA approval.

How is the Fat Used?

Lipogems® is designed to process your body's own adipose tissue to harness its reparative abilities.

Fat, usually taken from the abdomen, is harvested by a plastic surgeon. This is done in precisely the same way that liposuction is performed. Because of the volume of fat being dramatically less than that removed in liposuction, it is called lipo-aspiration.

In order to be able to turn this fat into a usable product for regenerative therapies, a Lipogems® device is used to mechanically break the fat down into very small fragments. This process is also referred to as micro fragmentation. The fat is then washed to remove excess oils and blood as these can be a source of irritation when injected into areas where the therapeutic potential is to be utilised. Following this process, the micro fragmented fat is then ready for use at the operative site. The multipotent cells derived from the Lipogems® device can stimulate your body's repair mechanisms in many tissue types. Research has shown that adipose tissue has the potential to treat a variety of problems across multiple disciplines.

What the research shows - a mini literature review

1.1 Safety and efficacy

The Lipogems® system is one of the ways to produce micro fragmented fat for use during a surgical procedure. It has proven to be safe and its simplicity has meant the indications for its use have expanded over the years.

In 2013 Bianchi, et al. [3] demonstrated that unlike the currently available techniques dependent on enzymatic digestion to attain clinically viable adipose tissue, Lipogems® required no cell expansion and no extensive manipulation. This meant that clinical translation of the potential multipotency of adipose tissue would not be delayed due to the frustrations of ex vivo expansion and the complexity of cGMP (current Good Manufacturing Practice) conditions for expanded cells. Without the need for enzyme involvement and cell expansion Bianchi and colleagues further showed that the Lipogems® product retained a preserved vascular stroma. Using immunohistochemistry and flow cytometry the team were able to reveal that the preserved stromal vascular tissue comprised of a higher abundance of cells with pericyte and hMSC identity compared with lipoaspirates that were enzymatically digested. These findings were supported and built upon by others throughout the literature. Cryopreservation was found by others to not diminish the quality of the Lipogems® product, the vascular stroma is preserved both before and after [4]. Thus the ability to harvest and freeze adipose tissue progenitors when young may maintain their higher regenerative and therapeutic capability [5] [6] [7]. Carelli, et al. [8] established an increased expression of self-renewing antigens and neural phenotypic genes in pericyte and hMSC cells derived by Lipogems®. These key discoveries demonstrated the safety and time efficiency of the Lipogems® procedure and its potential to be utilised in varying medical fields for novel approaches in small- and large-scale regenerative medicine [9].

These key discoveries have demonstrated the safety and time efficiency of the Lipogems® system as well as its potential for use in a number of medical fields [9].

1.2 Orthopeadics

One of the most common uses for micro fragmented fat is in orthopaedics [10]. The investigations have been in the treatment of pain due to degenerative conditions and as an adjunct for the treatment of sports injuries. Over the past decade researchers have observed that pain can be significantly reduced and function improved in patients suffering from osteoarthritis through intra-articular injection of adipose derived cells.

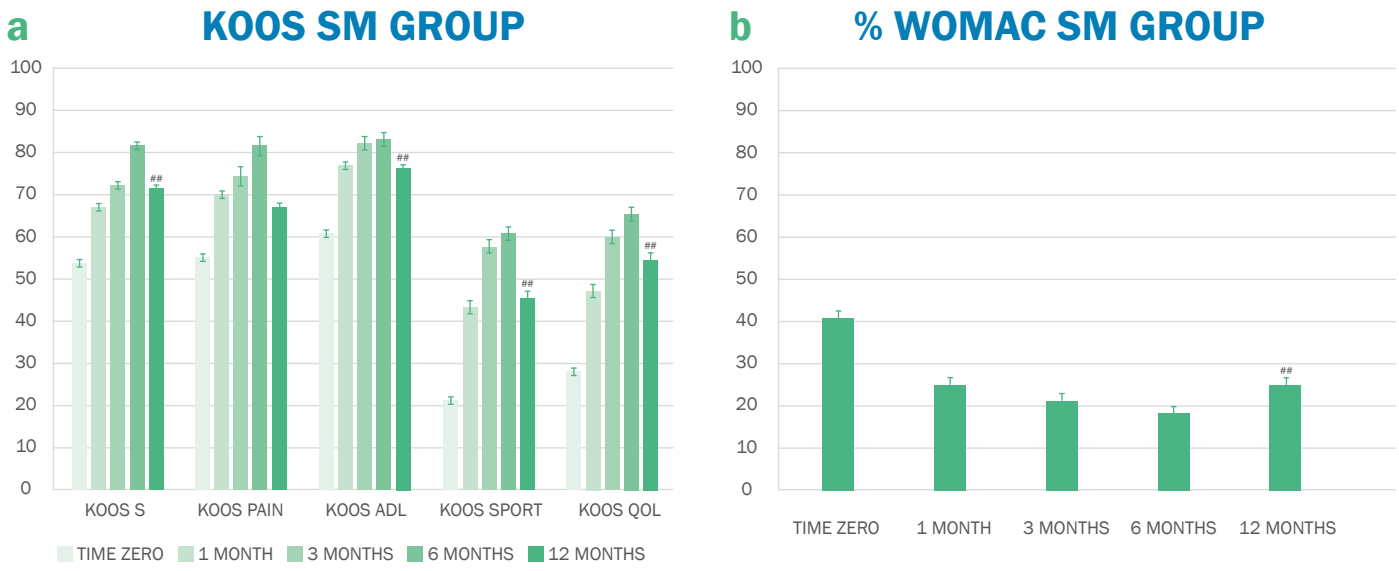
Collectively the results of the studies demonstrate that adipose derived cells can be used to increase proteoglycan levels within cartilage and stimulate immunomodulatory responses which reduce inflammation within the joint leading to a reduction in pain. Hudetz, et al. [11] treated 32 knees (17 patients) with OA using Lipogems®. No adverse effects were reported at the 12 months follow-up and patients exhibited a significant reduction in pain at rest and with activity (Table 1), these findings were mirrored in the studies by Cattaneo, et al. [12] (Figure 1) and Panchal, et al. [13].

Table 1 - Basic clinical comparison of Lipogems® treatment for KOA across the different follow-up times [1]

	Initial (M0)	First Follow-up (M3)	Second Follow-up (M6)	Third Follow-up (M12)	p* (M0-M3)	p* (M0-M6)	p* (M0-M12)
C-reactive protein (CRP) mean ± SD (min-max)	6.54 ± 7.83 (1-20.3)	-	3.86 ± 3.71 (0.6 -12)	5.17 ± 5.83 (0.6-23.1)	-	0.158	0.330
Visual analogue scale pain rating; resting; mean ± SD (min-max)	3.94 ± 2.56 (0-8)	1.24 ± 1.48 (0-4)	1.17 ± 1.62 (0-5)	0.56 ± 1.2 (0-4)	0.001	<0.001	<0.001
Visual analogue scale pain rating, movement; mean ± SD (min-max)	7.33 ± 1.72 (4-10)	3.82 ± 2.07 (1-7)	3.67 ± 2.03 (0-7)	3.17 ± 1.98 (0-7)	<0.001	<0.001	<0.001

*Pair-wise testing with t-test for paired samples; SD: standard deviation; M: months.

Figure 1 - Trend of functional improvements from baseline to 12 months follow-up, using different KOOS scoring [12]



Furthermore, the VAS and clinical results, were accomponied by increased presence of GAG (glycosaminoglycan) in hyaline cartilage (measured by dGEMRIC MRI) which could be seen as an increase in the joint space and minor correction of the limb axis.

Successful use of Lipogems® in the treatment of knee arthritis led to its use in treating degenerative conditions in other joints. Striano, et al. [14] showed positive results in shoulder OA with significant pain reduction, increased functionality and improved quality of life which was sustained at the 12 month follow-up. They did not report any adverse events or complications. (Figure 2)

Pak et al. [15], reported significant MRI changes, which accompanied positive outcomes in a patient suffering OA of the hip joint. Dall'Oca, et al. [16] also published positive outcomes (6 patients) for treatment of hip OA with Lipogems®.

Interestingly the regenerative effects of both bone marrow and microfragmented fat seems to be enhanced when the two are combined with improved capacity for self-healing in a range of osteo-articular tissues (ankle, knee, and shoulder) [17].

1.3 Aesthetics

The early use of Lipogems® has been in aesthetic and maxillofacial surgery. It has been used alone and in conjunction with traditional surgical techniques. It improves and accelerates natural wound healing.

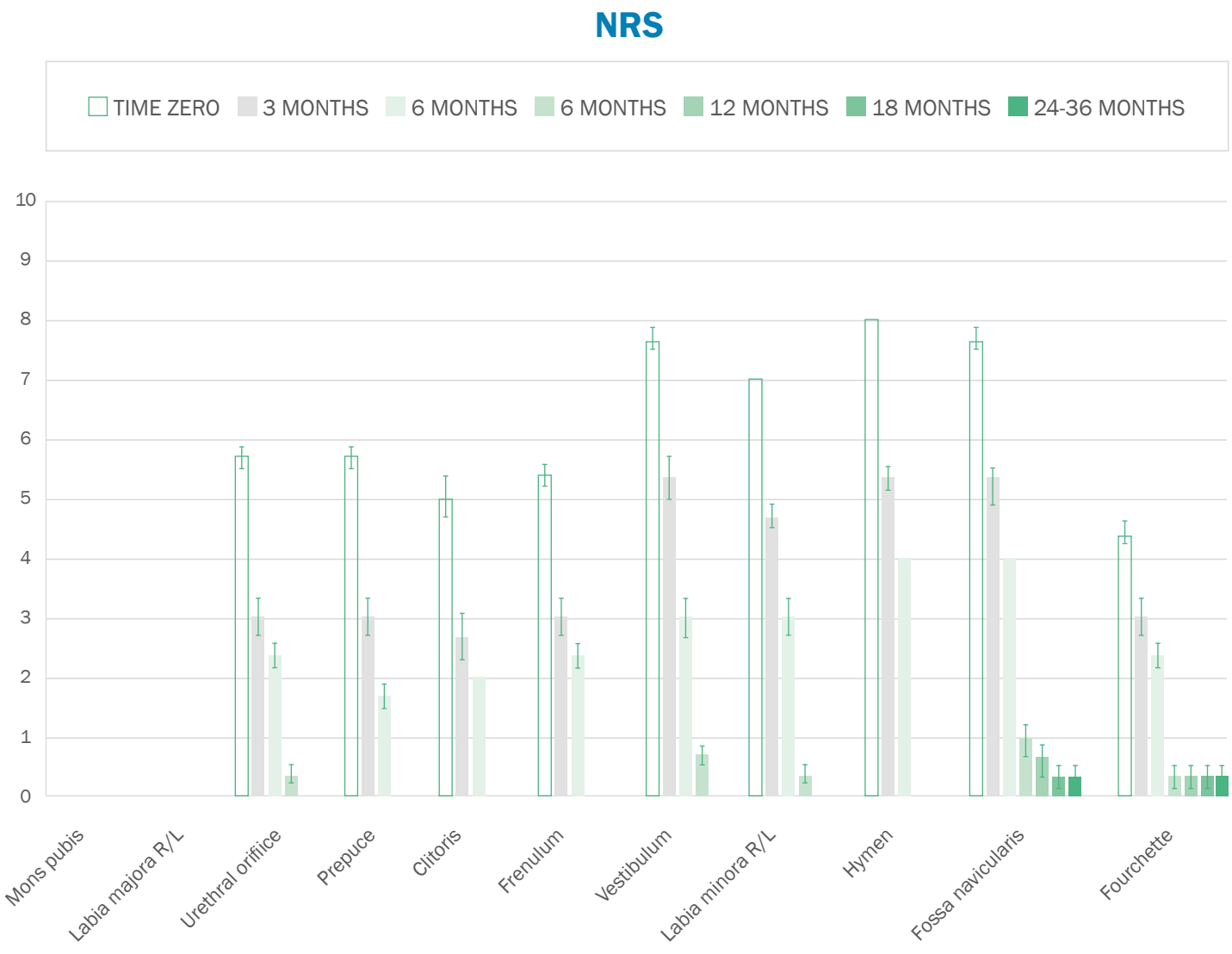
Raffaini & Tremolada [18] treated 120 patients with Lipogems® as part of their facial surgery: at the 12-month follow up all patients exhibited satisfactory results regarding facial morphology and the textural composition of the skin. The team went on to further compare these results with a past series of patients (903) that received alternative lipofilling techniques. The comparison showed that immediate post-op pain and inflammatory response was greatly reduced in the Lipogems® patients, whilst the long term results identified minor reabsorption and almost no tissue irregularities. Similar findings have been mirrored in reports by other investigators with improved healing, reduced inflammation, infection and swelling [19] [20]

1.4 Gynaecology

Lipogems® has been used with great success in relieving symptoms of post-menopausal vaginal atrophy.

Both Fantasia, et al. [27] and Casarotti, et al. [28] reported in their published papers how the epithelium and subcutaneous tissue of the vagina regenerated accompanied by a dramatic reduction in symptoms. Casarotti and colleagues followed their 3 patients for a total of 36 months, evaluating a range of criteria (vaginal dryness, itching, sensitivity, dyspareunia, and more) in addition to biopsies and vaginal discharge collected prior to and after the treatment. Significant improvements in symptoms were experienced by all women at 6 months and complete resolution of their problems by 9 months, which did not recur at the last review at 36 months. Laboratory evaluation of biopsies confirmed the return of an almost normal mucosa with glycogen production, hyperplasia of vasculature, epithelial and subcutaneous regeneration.

Figure 4 - Intensity of dyspareunia reported with the numerical rating scale for pain pre- and post-procedure [28]



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What does The Regenerative Clinic do?

The Regenerative Clinic is a global clinic that is leading the way in regenerative medicine.

At the Clinic, we understand the benefits of Lipogems® as a regenerative treatment and have a team of experts in orthopaedics, aesthetics and gynaecology who want to help alleviate patient pain and symptoms in a way that is best for them.

We are invested in patient care - we aim to provide constant guidance, support and expertise throughout the treatment process from consultation through to rehabilitation. Our dedicated team of experts are equipped to offer traditional treatments including surgery, but also cutting edge regenerative treatments, such as Lipogems®, that look to avoid surgery and optimise the body's own natural healing capabilities.

What is The Regenerative Clinic working on?

We are committed to the advancement of medicine to ensure our patients receive the best care and treatment available. We therefore understand the importance of researching our regenerative treatments and measuring outcomes.

As part of our service we provide on-going assessment and monitoring of our patients' progress; all the data is stored and analysed, generating results that will feed back into the medical treatments and processes we provide.

The clinic is working closely with the University of Winchester to carry out vital research in the field of health and wellbeing, including regenerative medicine.

In the past we have been involved in the set up and running of the Knee Preservation Foundation, in a collaborative environment established to explore innovative theories regarding knee related surgery, whilst providing patients and colleagues a platform to discuss their personal experiences. This has led to a hub for research and innovation, in which the sharing of knowledge has benefited academic understanding and clinical practice in the field of knee preservation.

The success of this venture has driven us to become more involved in research. Currently we are running a range of projects, from retrospective clinical audits to supervision of PhD student research.

Most notably we are working towards a large scale study that is looking at the long-term benefits and outcomes of Lipogems® in joint preservation. We are collecting a wealth of clinical data from patients pre- and post-treatment as well as medical history, demographic data and intra-procedural information in order to carry out advanced analysis and sub-analysis.

Our current findings in orthopaedics have been better than expected, showing positive responses as early as 3 months after treatment with micro-fragmented adipose tissue for patients suffering knee osteoarthritis (pre-op VAS >5). Long term assessment and follow-up at one year has demonstrated that over 80% of 84 patients experienced a significant reduction in pain and an increase in functionality, with the Oxford Knee Scores seeing improvement ($p<0.001$) from a mean value of 21.2±5.66, at 3 (31.3±9.64), 6 (29.7±10.3), and 12 months (30.9±8.16) and VAS scores for pain halving (from 'intense' to 'tolerable') with improvement ($p<0.001$) from a mean value of 6.86±1.48, at 3 (3.71±2.67), 6 (3.67±2.82), and 12 months (3.54±3.12).

The results from this investigative work have proved invaluable, establishing validity of the amazing novel treatments used at the clinic.

Collection, storage and complex assessment of such huge data sets has identified the need for more advanced medical software than is currently available. A new application is required, capable of not only storing patient data and ensuring management of patients but also able to perform complex analytics to produce relevant results. This has lead The Regenerative Clinic, in collaboration with the University of Winchester's Health and Wellbeing Research Group, to design and develop a new outcomes application tool that will meet these modern clinical needs.

We are in the process of applying for funding to get this project up and running. Once finished, the product will ensure that the efficacy of novel treatments in orthopaedics - and a range of other medical disciplines - can be evaluated and validated. The long-term impact will be to improve patient outcomes and thereby quality of life.

Our collaboration with research institutions, companies, and key experts in their fields has been paramount to the advancement of regenerative medicine and joint preservation treatments. Building on what we have done so far we endeavour to continue expanding our international network to ensure that important research - that has patient care at its focus - is conducted.

Six month VAS and OHS Results

Six month VAS and OHS Results of Patients treated with Lipogem® Treatment at The Regenerative Clinic UK.

At The Regenerative Clinic, we have treated 26 hip joints with six month results following Lipogem® treatment. We have assessed patients' responses at 3 months and 6 months following their treatment. Our findings show that 17 out of 26 patients have had a dramatic response, while just 9 have not responded; this means that 66% of our hip patients have seen an improvement in their functional outcomes and in their pain scores.[i]

The methodology used to determine patient's pain levels is the Visual Analogue Scale (VAS).[ii] On average, patients come to us with VAS pain levels of 52. Patients then fall into two groups; those that respond and those that do not respond. In those that respond we have found that, 6 months after treatment, their average pain scale falls to just 9 out of 100.

This indicates that, for these patients, the Lipogem® treatment was significantly successful and corresponded to a dramatic fall in pain levels. The 9 patients who did not respond had a mean VAS score of 47 prior to treatment, slightly less than the overall group average.[iii] After treatment, the non-responsive patients' average scores increased to 60 and have remained at this level for 6 months. It is likely that this is due to the natural progression of the disease in these arthritic hips and not due to the treatment itself.

Another method which we use to measure the functional outcome of our Lipogem® treatment is the Oxford Hip Score (OHS).[IV]

This is a questionnaire which assesses how the arthritis of the hip is affecting the function of the patient, and to make judgements about the severity of their symptoms. The OHS places each patient on a scale from 0 (a poor OHS score) to 48 (an excellent OHS score). The average OHS of the patients we have treated is approximately 28.[v] In the group that have responded to the Lipogem® injections, their OHS has improved from 28 to 43, a normal level of function for the majority of people. The group that has not responded, who had a functional score of 30 before treatment, have been reported to have maintained a very similar score (an avg. score of 37) six months later.

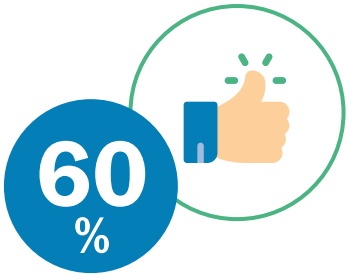
Our results show that the majority of patients treated with hip arthritis have seen positive responses, with a dramatic reduction in pain and a considerable improvement in functionality.[vi]

In the non-response group of patients, there is a group who have lost the ball and socket shape of the hip joint which dramatically reduces the likelihood of the biologics working. Whilst these patients were advised that the Lipogem® treatment would not be a suitable treatment considering the level of mechanical degradation, this was still their preferred option. Likewise, despite being advised against the procedure, two patients had a severe phobia of surgery and therefore would not consider any other type of intervention.

i See Graph 1.1 Above with 6 month Visual Analog Scale (VAS) accumulated May 2019 by R&D Copyright The Regenerative Clinic 2019.
ii See Graph 1.1 Above with 6 month Visual Analog Scale (VAS) accumulated May 2019 by R&D Copyright The Regenerative Clinic 2019.
iii See Graph 1.1 Above with 6 month Visual Analog Scale (VAS) accumulated May 2019 by R&D Copyright The Regenerative Clinic 2019.
iv See Graph 1.2 Above with 6 month Oxford Hip Score (OHS) accumulated May 2019 by R&D Copyright The Regenerative Clinic 2019.
v See Graph 1.2 Above with 6 month Oxford Hip Score (OHS) accumulated May 2019 by R&D Copyright The Regenerative Clinic 2019.
vi See Graph 1.2 Above with 6 month Oxford Hip Score (OHS) accumulated May 2019 by R&D Copyright The Regenerative Clinic 2019.

Six Month Hip Score Outcome

hips treated



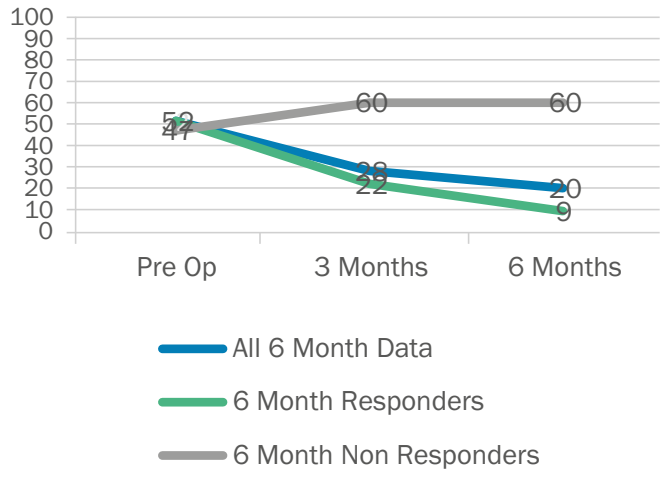
response rate

Comments:
Responders show continued improvements according to OKS: **consistent for up to 6 months**

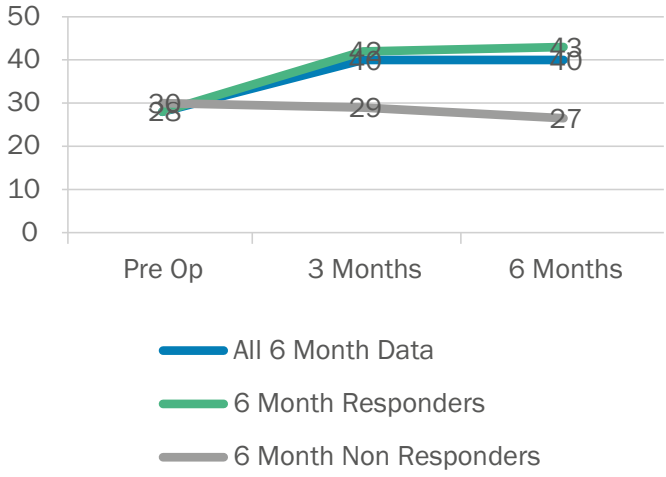
Visual Analog Score

Graph 1.1

VAS *N = 26*



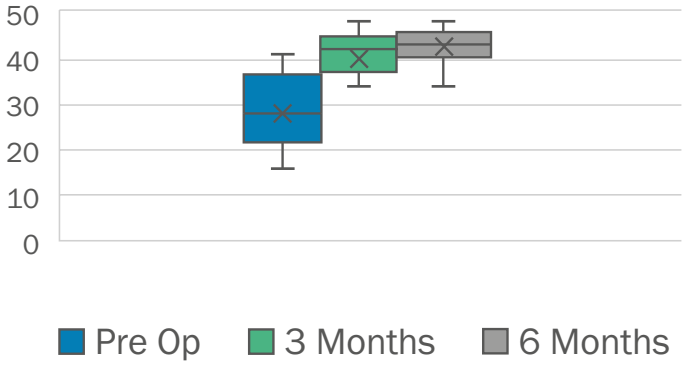
OHS *N = 26*



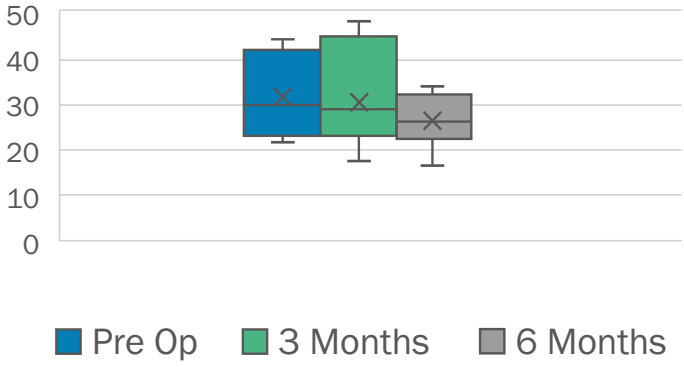
Oxford Hip Score

Graph 1.2

Responders (N=17)



Non-Responders (N=9)



One Year Knee Outcome VAS and OKS Results

One Year Knee Outcome VAS and OKS Results of Patients treated with Lipogem® Treatment at The Regenerative Clinic UK.

The Regenerative Clinic have used Lipogems® to treat knee arthritis for almost two years. Over this time, our clinic has successfully collected data on the patients that have been treated. Significantly, we now have one-year, post-procedure follow-up data for 42 patients that suffered from arthritis in their knee joint/s.

The Regenerative Clinic have an expert research team that measure patient responses to the Lipogems® treatment in two distinct ways: Using a Visual Analogue Scale (VAS) and the Oxford Knee Score (OKS). These are both validated ways of objectively measuring the outcomes of our treatments.

The VAS measures the level of the patient's pain between 0-100; 0 = no pain and 100 = max imaginable pain.

The OKS measures the functionality of the joint between 0-48; 0 = no function at all and 48 = best possible functionality

We measured these outcomes at various time points following the treatment. We start collecting data pre-procedure and continue to follow up with the patient at 3 months, 6 months and 12 months post-procedure.

The results of the VAS of 42 patients treated show that 35 patients (i.e. 83%) have responded to our treatment. This means that, by the 12-month mark after the procedure, their degree of pain is less than the pain that they had prior to the treatment. On average, patients come to us with a pain score of 75. This has improved to a score in the region between 20-30. This equates to an improvement of over 60%. It is important to note that there are individuals who have not responded to the Lipogems® treatment. Although they may have initially had a reduction in pain in the initial 3-6 months, this was not maintained at the 1-year mark. The reasons for this are not entirely clear and may be multifactorial, which is why we are still continuously collecting data from every patient that has the Lipogems® procedure.

In terms of the OKS results, we found a similar rate of response as the VAS results. 33 patients responded, which equates to 79%. 2 people did not complete the OKS scores, but these 2 were responders on the VAS data. We found that on average patients came to us with an OKS below 20 and by the 1-year mark this increased to approximately 35. These results are comparable with having a total knee replacement, but without any complications that are associated with surgery.

7 of the participants OKS scores remained constant throughout (i.e. their mean OKS remained between 20-25, where it started out from), thus no change in symptoms was witnessed in this group.

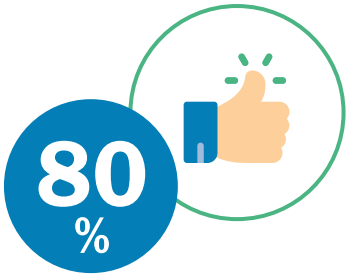
The deterioration that can be seen on the graph is presumably due to the natural progression of the arthritis disease and has no correlation to the Lipogem® treatment.

The severity of arthritis on x-ray's can be graded using the Kellgren-Lawrence system of radiological classification. We found that most patients that we have treated, presented with the most severe grading of arthritis on their x-ray's. The response witnessed in these patients has shown to be similar to those who have less severe forms of arthritis. It can be inferred from this information that the vast majority of patients have actually responded to the treatment. For example, in our grade IV group, which concerns the patients presenting with the most severe arthritis, we have treated 25 individuals. Of these, only 2 have not responded to Lipogems®.

In conclusion, our results demonstrate that over 80% of patients have responded to their Lipogems® treatment for arthritic knees. This response has been dramatic and equivalent to those who opt for a total knee replacement. Significantly, the patients that opted for Lipogems® saw the same results without the complications and risks of having operative surgery

One Year Knee Score Outcome

knee's treated



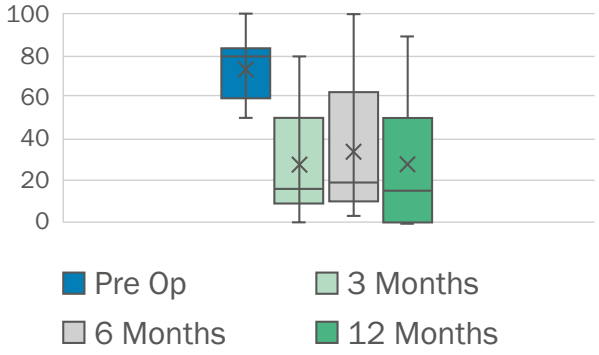
response rate

Comments:
Responders show continued improvements according to OKS: **consistent for up to One Year.**

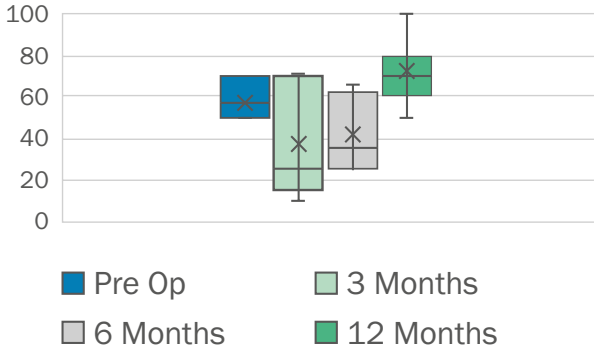
Visual Analog Score

Graph 1.1

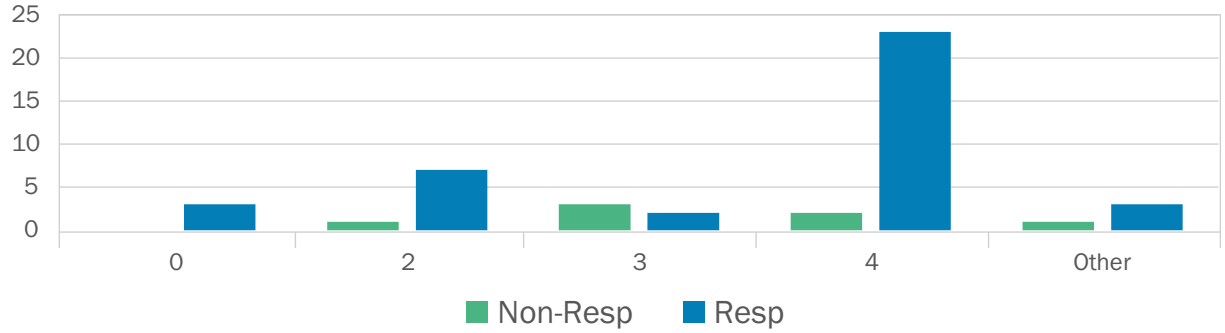
Responders (N=35)



Non Responders (N=7)



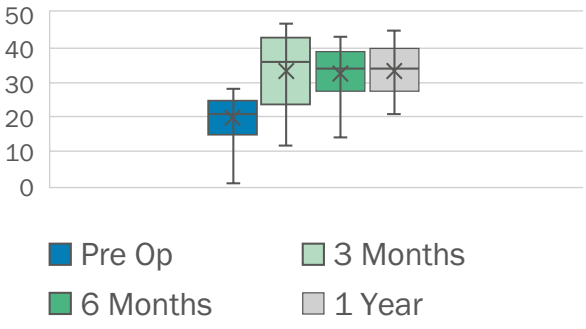
Response Rate by OA Grading



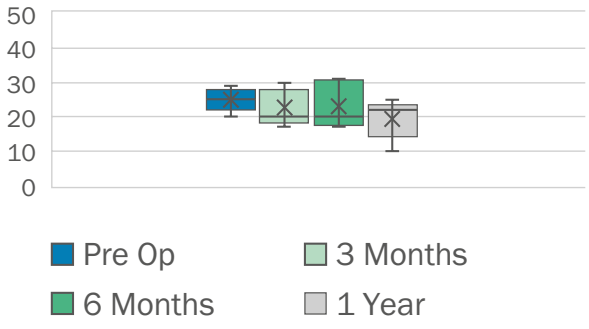
Oxford Knee Score

Graph 1.2

Responders (N=33)



Responders (N=7)



The Regenerative Clinic