Building rings with spheres: a cell therapy approach to incontinence

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Fecal incontinence is a prevalent condition, that remains vastly underreported. The condition impacts the patients’ quality of life and has negative socio-economic and environmental impact on the society. Current patient management guidelines recommend a step-wise approach to treating fecal incontinence, from conservative treatment options, through minimally invasive surgical options, all the way to first- and second-line surgical options. Unfortunately, the conservative treatments remain ineffective, and, in many cases, the surgical options are either not desirable or not suitable. Regenerative medicine, and specifically, cell therapy, has the potential to offer a curative treatment that is less invasive, more effective and efficient. Cell therapy technologies, while still under development, can improve the current state-of-play in the realm of fecal incontinence at the clinical, patient, and socio-economic level. The aim of this article is twofold. Firstly, it is to raise awareness about the silent affliction that fecal incontinence is and about the impact that it has on patients and society. Secondly, it is to position cell therapy, relative to the current treatment approaches, including, for example, sacral nerve stimulation and sphincteroplasty, as to emphasize its potential to provide a suitable treatment alternative.

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THE PROBLEM: FECAL INCONTINENCE IS A PREVALENT CONDITION THAT IS CURRENTLY LACKING APPROPRIATE TREATMENT OPTIONS

Fecal incontinence: a brief introduction to the condition

Fecal incontinence (FI) is a condition in which control of bowel movement is impaired, leading to leakage of feces. According to the symptomatic profile, FI is classified in three categories [1]:

1. Passive incontinence;
2. Urge incontinence;
3. Fecal seepage.

In case of passive incontinence, patients are unaware of the discharge that involuntarily arises due to overflow of the full rectum [2]. Passive incontinence indicates the malfunctioning of the anal sphincter, anorectal reflexes, or a neurological disease. As opposed to passive incontinence, urge incontinence occurs when patients consciously defecate while being unable to control sudden bowel movements [3]. Urge incontinence suggests impairment of the anal sphincter or the rectum to prevent discharge. Lastly, fecal seepage is the complication of involuntary discharge after the occurrence of normal continence and bowel movement [4]. The disruption of the anal organs, notably to the sphincter muscle that creates a ring structure around the anal canal, can be structural or functional, respectively meaning that FI has occurred after injury, trauma, or childbirth, or naturally due to neurological disorders [1].

While underreported, FI is a prevalent condition, most common in parous women, frail older patients and patients with neurological disorders

Although an estimation of European adults affected by FI is recognized, its precise and worldwide prevalence is unknown, as the lack of patients reporting their FI-related symptoms and diagnosis discrepant symptoms thus leads to a potentially underestimated prevalence of patients suffering from FI [5]. Despite lacking precise data, it is estimated that in Europe approximately 57 million adults are affected with FI [6]. Specifically, FI occurs in up to 15% of the Western population. Both men and women of all ages worldwide are affected by FI (Figure 1), and although FI in men has received little attention in the past, it is still as much of a problem in men as it is in women [7].

Groups with the highest incidence rates of FI are parous women with sphincter muscle damage or dysfunction, frail older patients, and patients with neurological or spinal disease/injury. These groups are described below, respectively.

Parous women may suffer from sphincter injury as a result of pregnancy and childbirth

It has been reported that 11% of postpartum women globally have sustained sphincter muscle injury [8]. While the prevalence is primarily studied in high-income countries [9], it is apparent that women from low- and middle-income countries (LMICs) are at a high risk of developing FI, too. Specifically,
women that develop uncommon communication between the gastrointestinal tract, the urinary tract and/or the genital tract, so-called obstetric fistulas (OF), during labor are at a higher risk of developing FI [9,10]. The majority of these OF cases are in sub-Saharan Africa and South Asia, followed by Latin America and the Caribbean [11]. Those affected by OF in low- and middle-income countries (LMICs) are young, primiparous, impoverished women that have little, or no access to health care [11]. Pregnancy and childbirth are risk factors for transient postpartum FI. Studies have shown that during pregnancy and childbirth, women encounter issues such as pelvic floor injury and stretching or tearing of the nerves, muscles, and supporting tissues [12]. Vacuum or forceps-assisted vaginal delivery is seen as a risk factor for developing FI as these methods increase the risk of anal sphincter ruptures [13]. There are studies that suggest that caesarean section protects against developing sphincter injury, specifically fecal incontinence beyond the postpartum period [14]. Of the 11% of women with sphincter muscle injury, between one-third and two-thirds will suffer from FI [8]. To illustrate the impact of this, of the 4.09 million women who gave birth in Europe in 2021 [15], 449,900 are likely to have a sphincter muscle injury, of which 150,000 to 300,000 will be affected by FI. The type of birth and delivery method also plays a role in the prevalence of FI in parous women [13]. In some cases, postpartum FI is only temporary and neuromuscular injury sometimes improves during the first year after giving birth [13], while in others the condition gets progressively worse due to the confounding effect of aging and the menopause.

Frail older patients have a high risk of bowel disturbances

FI in older patients can be a challenging and stigmatizing condition to deal with alone. Patients often do not seek help for their condition. The main risk factors for FI in the elderly include bowel disturbances such as diarrhea and irritable bowel syndrome (IBS) [4]. Bowel disturbances are more amenable to therapeutic intervention as they are often easier to correct than neuromuscular injuries to the pelvic floor [4]. Several causes have been reported for the onset of FI in frail older patients, of which examples include living a sedentary lifestyle or having a decreased fiber intake. No differences between sexes have been analyzed in older patients, as opposed to lower age groups that suffer from FI [16]. There are certain comorbidities associated with FI, such as diabetes mellitus, stroke, and neurological disorders [4]. Prevalence rates of FI increases in patients over the age of 50, among hospitalized patients and in patients that are institutionalized. According to a systematic review of older patients in care homes in Europe, approximately 50% of older people living in care homes are affected by FI, compared to an estimated 18% of the general population [17].

Patients with neurological injury or disorder suffer from disruption of nerves that control storage and excretion of waste

Other examples of patients suffering from FI include those with neurological disorders, metabolic disorders or other types of disorders that affect the functioning of the sphincter muscle. Individuals with a neurological disease have a higher risk of FI than the general population [18]. The nervous system controls storage and excretion of fecal waste, hence the disruption to the nerves enhances the likelihood to develop FI [19]. For example, the incidence of FI is higher in patients with multiple sclerosis, spinal cord injuries, cerebrovascular diseases, and Alzheimer’s disease [19,20]. Patients with dementia are prone to FI due to use of medication, dietary intolerance, or the decreased cortical control over stool release [21].
Current treatment options for treating FI are often either not effective, or not desirable and/or suitable

Current patient management guidelines recommend a stepwise approach to treating FI—from conservative treatment options, through minimally invasive surgical options, all the way to first- and second-line surgical options (Figure 2). Conservative treatments designed to minimize symptoms are typically used in first-line therapy, especially in those with mild symptoms. Such treatment options include dietary modifications, patient education, bowel management exercises, biofeedback and anti-diarrheal or anti-motility medication [22]. If conservative treatments do not have the desired effect (estimated to fail in 40–75% of the cases), patients will be treated with minimally invasive options including injections of bulking agents, balloon devices, posterior tibial nerve stimulation, transanal irrigation and radiofrequency therapy [6,23]. In case of ineffective treatment by means of non-surgical options, first-line and second-line surgical options are proposed. In first-line surgical treatment, the sacral nerve is stimulated or sphincteroplasty is performed to strengthen weakened muscle areas [24]. Of the patients recommended for first-line surgical treatment, approximately 80–90% receive SNS and 10–20% undergo sphincteroplasty. The success rate of these treatment options is approximately 60% and 80%, respectively, with potential declining effect over time [25,26]. The efficiency of sphincteroplasty can be enhanced by magnetic sphincter augmentation [27]. The last resort is second-line surgical treatment, to create a colostomy, where stool into a collection bag is diverted through an opening in the abdomen.

The effectiveness of different treatment options for FI depends on the severity of the condition and the patient group. The treatment considerations differ for the three patient groups: parous women, frail older patients, and patients with neurological disorders. The most suitable stepwise approach for parous women is to first attempt conservative treatment (electrical stimulation of the pelvic floor muscles, physiotherapy, dietary management, etc.), and then minimally invasive and first-line surgical treatments (SNS). In frailty, patients are prescribed dietary modification or referred for the minimally invasive and first-line surgical treatments (SNS). For patients with neurological disorders, treatment depends on the symptoms but most often starts with conservative treatment options, such as bowel...
management programs. Unfortunately, conservative treatment options are generally ineffective and the patient undergoes surgical treatment. However, many patients do not wish to, or are unsuitable for undergoing surgery.

**FI impacts patients’ quality of life and has socio-economic and environmental implications on the society**

FI poses emotional & mental stress on patients’ lives

FI heavily affects the quality of life (QoL) of affected individuals. Lifestyle, social interaction, coping behavior, depression or self-perception, and level of embarrassment are aspects of the QoL of FI patients that are influenced by several FI severity factors (i.e., frequency of soiling, quantity and type of fecal loss, and urgency) to different degrees [28]. Due to the associated social stigma of FI, it is often deemed as the ‘silent affliction’ [29] or the ‘unvoiced symptom’ [30]. Topics that breach social norms about bodily functions are often regarded as something that should be discussed in private. The fact that patients are aware of the public stigma makes them develop self-stigma, i.e., they internalize the public’s negative reactions and interpret the stereotypes as true and accurate. This can lead to the avoidance of help-seeking [31]. Those with mild symptoms may be unwilling to realize that they are experiencing FI symptoms; and those that eventually come to terms with a diagnosis are reluctant to share it with others and seek further help from health care professionals [32]. Approximately 70% of patients with FI do not reach out for medical help [28]. Moreover, FI can lead to social isolation and has an impact on intimate relationships and self-esteem [33]. For example, despite the partners and spouses being generally supportive of their partners’ diagnosis, they have also reported avoiding intimate and sexual activities with the affected individual [33].

**FI imposes significant costs both for patients and society**

Patients suffering from FI have substantial medical costs. Firstly, this includes expenditure for incontinence products, medications, and other healthcare products [34]; secondly, costs are incurred due to greater frequency of health care practitioner visits, which includes costs of transportation, costs of the consultations [33]. Patients with FI have on average 4.21 more healthcare visits per year than patients without FI [35]. Moreover, FI patients need support in their day-to-day activities, in particular, frail older patients that need nursing support. While more recent statistics are not available, in 2012, the average annual cost per person was €4,110, including direct medical and non-medical costs and indirect costs for productivity loss [36]. This causes an overall economic burden, as the money could otherwise be invested elsewhere [35]. Regarding the financial impact to society, affected individuals become less active through increased days off, loss of productivity, and higher rates of unemployment and absenteeism [37]. Considering the EU as the relevant population for this article, patients with large-volume FI report missing an average of 50 days from work or school annually, relative to those individuals without FI symptoms [37].

**FI imposes environmental costs due to the increasing use of medication and products**

Patients with FI use a wide range of medications and hygienic products. In Europe, the contamination of groundwater is enhanced due to the increasing use of medication [38], with anti-diarrheal medication reportedly being found in groundwater [39]. With the rising need for incontinence products (e.g., pads or diapers), the energy consumption and carbon emissions increase [40]. Similarly, as the products often contain non-biodegradable material, the environmental pollution increases too [41].
Overall, without effective treatments, parous women, frail older patients and patients with neurological disorders suffering from FI will continue experiencing a decreased QoL and the condition has significant economic and environmental impacts on society.

THE SOLUTION: A CURATIVE TREATMENT DECREASING THE BURDEN ON PATIENTS’ LIVES & ON SOCIETY

Conservative treatment options are generally ineffective and patients are often referred to undergo different kinds of surgical treatments. While surgical sphincter repair is the most successful improvement of continence, it does not always persist in the long-term [42]. Hence, regenerative medicine approaches have been under investigation as a novel alternative approach due to their success in the treatment of other indications (e.g., hematological, cardiovascular, neurological, digestive, traumatic, endocrine, renal, and metabolic conditions) [42].

Regenerative medicine products

Regenerative medicine aims to restore tissue that is impaired due to injury, aging or disease [43]. Treating fecal incontinence with regenerative medicine is at its infancy, there is a lot more within the field to be explored and developed. While the development of regenerative medicine in the relatively new realm of FI is rather fast, it is still lagging relative to other indications [43]. Among else, this is due to the stigma associated with FI, resulting in patients’ reluctance to openly discuss the condition [31]. Consequently, the potential of patient recruitment for clinical trials is limited. Moreover, in the context of sphincter defects, it remains difficult to understand the choice of suitable biomaterial, the cell behavior following implantation and other technological aspects [43]. The most common approaches in the field of regenerative medicine include injection of biomaterials, tissue engineering, cell therapy, and a combination of the therapies [43]. The focus of this article has been narrowed down to, specifically, cell therapy, due to the vast potential that the approach shows in treating FI. While cell therapies for treating FI are still under development, the plethora of ongoing studies shows a clear positive signal regarding their potential as an alternative FI treatment. While the rest of the article focuses specifically on cell therapy, for the sake of completeness, the section below presents an overview of the four different regenerative medicine approaches.

Biomaterials can be used for injection into the anal sphincter to promote the restoration. Biomaterials include materials such as polymer, ceramics, metal, and composite materials [44]. Bulking agents are one type of biomaterial and can be inserted into the individual under local, regional, or general anesthesia. The injection depends very much on the type of clinical indication as well as the substance used. Bulking agents are intended to expand the tissue in the anal canal and prevent fecal leakage [45]. They can be performed in an outpatient setting with a low risk of morbidity, therefore increasing in popularity [45]. The use of bulking agents results in less frequent episodes of fecal incontinence over time as they can guide the healing process [46]. Some examples of bulking agents include the silicon biomaterial (PTQ), carbon-coated microsphere (DuraspHERE®), and the dextranomer in stabilized hyaluronic acid, also known as NASHA Dx [47]. Among those that are currently utilized, the NASHA Dx is the bulking agent that has shown to be most successful. This agent is approved for use in the USA and was trialed in Europe and in the USA in 2011. The result of the bulking agent was a >50% reduction in incontinence episodes, a 50% or greater reduction in incontinence episodes in 52% of the therapeutic treatment group compared to 31% in the placebo group at a 6-month interval [47]. Follow-up at 12 months presented a 50% or more reduction in FI episodes in 69% of patients in the therapeutic group,
whilst the placebo group were not measured at 12 months [47]. In 2013, the efficacy of all injectable bulking agents was measured, and it was concluded that the NASHA Dx injectable demonstrated a significant improvement in continence [47].

Tissue engineering is an approach that evolved from the field of biomaterials which involves the growth of functional organs in vitro that are then implanted into the body [43]. The goal of tissue engineering is to restore, maintain or improve damaged tissue and organs. Further research should enlighten upon the clinical application of tissue engineering in patients with fecal incontinence. So far, the vascularization and integration of the engineered tissue are challenges that yet need to be overcome before patients can be treated by means of tissue engineering [48].

Although it is stated that the cells’ environment and thus cell differentiation can be carefully regulated [49], some of the disadvantages of tissue engineering include the risk of tumorigenicity, immunogenicity, graft rejection and cell migration [50]. Additionally, vascularization of the site of implantation is potentially limited and the formation of the implantation requires time [43]. Autologous tissue repair showed to be an effective surgery. The advantages of autologous tissue repair include a minimal to moderate inflammatory response as well as a good integration with host tissues, however a disadvantage includes a high recurrence rate [51].

Cell therapy is a relatively novel, long-lasting, and effective regenerative therapy that uses stem cells for the purpose of tissue regeneration. This makes it a very interesting option to identify potentially curative treatments for FI when linked to damaged sphincter muscles. In the context of FI, there are no approved cell therapies yet, but the ones under development use autologous cells (i.e. patient’s own cells) and relocate them to the site of damage to repair the sphincter muscle. Cell therapy uses a variety of stem cell types, most commonly mesenchymal stem cells that can be obtained from a variety of tissues, often bone marrow, adipose or muscle tissue [52,53]. Autologous skeletal muscle derived cells (ASMDCs) are the most common cell types, these are obtained from the isolation of satellite cells from skeletal muscle biopsies that after processing can become myogenic progenitor cells [54]. These ASMDC can regenerate skeletal muscle cells to repair the external anal sphincter muscle. The current cell therapies under development for FI could be of benefit to patients with urinary incontinence [55,56], but also patients with joint or other muscle injuries [52,57]. A study showed that patients with limited FI duration and high incontinence episode frequency (IEF) are most responsive to cells [58]. Unfortunately, the survival rate of cultured cells is influenced due to the altered immunogenicity occurring during the ex vivo culturing period [43]. In addition, it is evident that routine use of cell therapy involves high costs [59]. A more cost-effective method for cell transplantation for anal sphincter regeneration has been proposed. Rather than expanding cells into injured anal sphincters, fragmented muscle fibers could be injected [60].

Cell therapy can be combined with biomaterials that provide a scaffold structure that can protect cells and then increase the chances of engraftment to form functional tissue [43]. When they are isolated from the patient, the cells are cultured in vitro and, in the case of FI, can be injected in combination with stimulating biomaterials to facilitate the functionality and attachment of the ASMDCs to the damaged site of the anal sphincter. Hence, the microenvironment is of upmost importance to sustain the quality of the ASMDCs. Studies have shown that presence of a scaffold has proven beneficial for the proliferation and myogenic ability of satellite cells [61]. Since ASMDC are at a more advanced differentiation stage than satellite cells, the importance of scaffold could be greater for this cell type [61]. Studies
researching cell therapy in combination with biomaterials have proved promising results, due to the ability of the created microenvironment to sustain the implanted cells. Although it is difficult to maintain a promotive microenvironment to sustain the quality of the ASMDCs, many technologies are emerging with the aim to improve the conditions of patients with FI [62]. In the following section we report on the competitive landscape of cell therapies in the field of FI as these therapies have been gaining more popularity over the past few years.

**Competitive landscape within cell therapy**

By December 2022, the US Food and Drug Administration (FDA) had approved a total of 27 cell and gene therapies [63]. The FDA anticipate approving another 10–20 therapies each year by 2025 [63]. Worldwide, the UK has the third largest cluster for cell and gene therapy production. In 2021, there were a total of 168 ongoing trials which made up around 9% of all global trials [64]. As of 2021, there have been a total of 16 new approvals of cell and gene therapies by the European Medicines Agency (EMA), of which 12 have been granted marketing authorization by the Medicines and Healthcare products Regulatory Agency (MHRA) [64]. Among the emerging technologies intended for FI cell therapy, a few have explored the use of microcarriers alongside different cell types. A comparison of the existing technologies based on stage of development, presence of the scaffold and intellectual property (IP) protection of the technologies is presented in Table 1 [65–67]. Notably, the most advanced therapies currently in phase 3 clinical trials are cell therapy approaches that do not use scaffold technologies. Conversely, the published studies on FI cell therapy with the use of scaffolds are relatively outdated and seem to have paused at the ical stage. The emerging technology with the most competitive advantage is the one developed by Innovacell, an Austrian start-up that has a broad IP coverage and a product at an advanced clinical development phase (phase 3 trials). Emerging evidence suggests that several cell therapies are seen as safe, however their therapeutic application and effectiveness remains a challenge [68].

**IMPACT: INTRODUCTION OF NEW CELL THERAPY TECHNOLOGIES WILL IMPROVE THE CURRENT STATE-OF-PLAY IN FI AT THE CLINICAL, PATIENT, & SOCIO-ECONOMIC LEVEL**

**Clinical level: expansion of available treatment options**

Cell therapy technologies have the potential to significantly alter the paradigm of treatment for patients with sphincter damage and for elderly patients. The conservative treatment options are generally not effective enough and the patient is referred further to undergo the different kinds of surgical treatments [46,69], which are often unsuitable or undesirable. Treatment using regenerative medicine products need to be entirely safe to differentiate them from other surgical interventions. For instance, surgical sphincter repair carries a high risk of wound breakdown and infection [70] and can result in permanent stoma in some patients [71]. SNS has the downside of initial cost and necessity for ongoing (lifelong) therapy maintenance (with further cost e.g., for battery replacements) [72]. Cell therapy could be an effective alternative for these patient groups. Due to its lower invasiveness and associated risk of adverse events, it is seen as a breakthrough therapeutical option for these patient groups.

**Patient level: improvement of QoL for patients**

Cell therapy products have the potential to significantly improve the patients’ QoL. Quality of patients’ lives is shown to increase after a clinically successful treatment [73].
Cell therapy products will provide an alternative treatment option for those patients with severe FI that are not responding to conservative therapies, as described in more detail in the section above. These products have the potential advantage over other surgical interventions and conservative treatment methods. As such, they will be a better alternative for several patient groups. An effective clinical treatment would spare patients from risks and inconveniences, ultimately leading to a higher QoL [73].

### TABLE 1
Comparisons of key players in the field of cell therapy for FI.

<table>
<thead>
<tr>
<th>Entity</th>
<th>Cell type</th>
<th>Scaffold</th>
<th>Development phase</th>
<th>Patents</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMELIE</td>
<td>Autologous skeletal muscle derived cells</td>
<td>Poly DL-lactide-co-glycolide</td>
<td>Preclinical</td>
<td>1 European, 1 international</td>
<td>Amelie-project.eu</td>
</tr>
<tr>
<td>Seoul National University College of Medicine</td>
<td>Autologous myoblasts</td>
<td>bFGF-loaded polycaprolactone beads</td>
<td>Preclinical (dog)</td>
<td>Not found</td>
<td>[65]</td>
</tr>
<tr>
<td>University of Texas Southwestern Medical Center</td>
<td>Myogenic stem cells</td>
<td>Polyethylene glycol-based hydrogel matrix scaffold</td>
<td>Preclinical (rat)</td>
<td>Not found</td>
<td>[66]</td>
</tr>
<tr>
<td>University of Tampere</td>
<td>Human adipose stem cell</td>
<td>Bulkamid, a non-degradable viscoelastic water-based polymer</td>
<td>Preclinical (rat)</td>
<td>Not found</td>
<td>[67]</td>
</tr>
<tr>
<td>Yonsei University</td>
<td>Allogenic-adipose-derived mesenchymal stem cells</td>
<td>None, but in one patent they use chitin and ligament stem cells to promote collagen formulation</td>
<td>Phase 1 completed</td>
<td>2 Korean, 1 international</td>
<td>(NCT02384499)</td>
</tr>
<tr>
<td>Innovacell AG</td>
<td>Autologous skeletal muscle-derived cell</td>
<td>None</td>
<td>Phase 3 ongoing</td>
<td>6 European, 6 international</td>
<td>(NCT04976153)</td>
</tr>
<tr>
<td>Cook MyoSite</td>
<td>Itamocel autologous muscle-derived stem cell therapy</td>
<td>None</td>
<td>Phase 3 ongoing</td>
<td>Not found</td>
<td>(NCT05776277)</td>
</tr>
<tr>
<td>Andalusian Initiative for Advanced Therapies Cellf Bio LLC</td>
<td>Autologous mesenchymal stem cells from adipose tissue</td>
<td>None</td>
<td>Phase 2 completed</td>
<td>Not found</td>
<td>(NCT02292628)</td>
</tr>
<tr>
<td>Wake Forest University Health Sciences</td>
<td>Muscle fiber fragments that contain muscle precursor cells (MPCs)</td>
<td>None</td>
<td>N/A (procedural)</td>
<td>6 European, 11 international</td>
<td>(NCT05396456)</td>
</tr>
<tr>
<td>University Hospital, Rouen</td>
<td>Autologous muscle-derived progenitor cell injection</td>
<td>None</td>
<td>Phase 3 completed</td>
<td>3 European, 2 international</td>
<td>(NCT01523522)</td>
</tr>
</tbody>
</table>

Sources: desk research, Wheesbee, and clinicaltrials.gov. Query for clinicaltrials.gov: (regenerative medicine) OR (tissue regeneration) OR (regenerative therapy) OR (cell therapy) | faecal incontinence; Selected status: Not yet recruiting, Recruiting, Enrolling by invitation, and Active not recruiting.
Socio-economic level: reduction of the negative impact of FI on the economy

Treatment of FI with cell therapies would have the potential to create considerable savings for the EU and would increase the productivity of patients. An effective clinical treatment would allow patients to substantially reduce the medical costs associated with the condition, as well as enable FI patients to be economically contributing members in society. Considering the above-mentioned assumption of 2–5% market penetration, these are the predicted socio-economic impacts of cell therapy products targeting FI:

- The new treatments could save EU citizens between approximately €11.74 and €29.34 million per year for women affected by FI arising from obstetric sphincter injury and between approximately €65.90 and €164.75 million per year saved for all patients with FI in the EU; and

- The new treatments could save between 222,650–556,000 working days per year for women affected by FI arising from obstetric sphincter injury and 1.25–3.125 million working days per year saved for all patients with FI in the EU.

RECOMMENDATIONS & CONCLUSION

Where current therapies against FI often are not as effective as required, regenerative medicine often offer less invasive treatments and can be applied to a broad range of patients. Amongst regenerative medicine, new cell therapies are under development, reflecting positive signals for the field of FI. Exploring some of the recommendations below might further support the endeavors within the field of regenerative medicine, especially in the context of FI.

Technological improvements

Among the key obstacles in regenerative medicine therapies based on skeletal muscle-derived cells are insufficient cell count at delivery/survival and recapitulating the features of adult cells [42]. Both these hurdles could be tackled by integrating a biocompatible scaffold, potentially also releasing stimulatory molecules (e.g., growth factors and cytokines) to facilitate both delivery and functionality of the cells [42]. Additionally, most studies for the use of stem cell therapy for FI so far lacked potential for clinical translation [53]. This is thought to potentially be a consequence of the general focus on the external sphincter muscle regeneration and the lack of understanding of role of the internal sphincter muscle. This could potentially go as far as stimulating vascularization to ensure successful survival and regeneration [42,61]. Safety of the cell therapy approaches should be confirmed, as the replicative property of stem cells is associated with the risk of carcinogenicity. Results from ongoing long-term studies using the cell type of choice, ASM-DCs for FI in most cases, should be carefully monitored [42]. Finally, cellular therapy is costly, so once the technology is improved, their commercialization will depend on efficiently scaling up production of the therapy, potentially through the use of allogeneic cells (i.e. from healthy donors) [74].

Educating patients about different treatment options

Alongside the development of cell therapies that potentially offer a curative treatment for patients with FI, patients’ families and the society should be made aware of the arising treatment options. Few patients are informed of the different therapies that are available to treat incontinence. Clinicians should be involved not only in the development of new potentially curative cell therapy treatments, but also in the education of the patients regarding the available options. A more effective
treatment will eventually contribute to the reduction of the stigma associated with FI.

**Providing safe platform for discussion and raising awareness**

While the charities and patient groups active in the field of FI exist to provide the much-needed support to patients with FI, it still remains true that the disease is highly stigmatized and its prevalence underreported. A community-based approach providing a safe platform for discussion and sharing, combined with an educative element as described above, needs to be in place. Public information campaigns should emphasize that the condition is relatively common, especially among the groups that are at risk, for the lack of conversation around FI contributes to the public underestimation of its prevalence, making the experiences feel more alone and perpetuating the cycle of stigma further. Similarly, public-facing campaigns could include information on prophylactic actions that doctors might provide to patients in a clinical setting. It is crucial that there is a unified effort across the EU, or at least that such charitable efforts take place in all countries, so that the inequality among countries does not further exacerbate the negative effect on FI on patients. With an increased awareness and decreased stigma, patients may feel motivated not only to share with fellow patients and thus raise awareness further, but they might also feel more comfortable in participating in the clinical development of alternative treatments.

**REFERENCES**


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**AUTHORSHIP & CONFLICT OF INTEREST**

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