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Data Article

Patient Perspectives on Use of Stem Cells to Treat Osteoporosis

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Abstract

Osteoporosis is a systemic skeletal disease leading to increased risk of fragility fractures. These fractures lead to significant patient morbidity, increased mortality and substantial health and social care costs.

The use of stem cells for cell-based therapies is currently an exciting, promising and growing area for disease treatment and regenerative medicine. However, the attitudes of participants towards the use of stem cells for regenerative medicine applications, particularly for therapeutic interventions amongst the older population, have not been well explored.

This study explored patient perceptions of a proposed new treatment utilising a novel orthobiologic stem cell therapy. An online questionnaire for participants affected by

osteoporosis was designed using the 'Bristol Online Survey' tool. In addition, three focus groups were held to explore a number of the issues raised by the findings in more depth.

Findings showed that acceptability for the new treatment was high, as current treatments were variable in their effectiveness and new treatments were keenly welcomed. Participants indicated a willingness to have the proposed treatment in order to reduce their chance of experiencing a fracture, regardless of whether the treatment would reduce existing pain, or improve existing quality of life. The use of both autologous and allogeneic stem cells was acceptable, with slight differences in opinion indicating reservations regarding the potentially painful nature of stem cell extraction and allogeneic stem cell rejection.

The findings demonstrated a clear mandate to the research team (and community) to continue their efforts in developing stem cell-based treatments for bone repair applications.

Keywords

Patient Public Perceptions; Osteoporosis; Stem Cells; Orthobiologic Therapy

Introduction

Osteoporosis is a systemic skeletal disease leading to increased risk of fragility fractures. These fractures lead to significant patient morbidity, increased mortality and substantial health and social care costs. Between 2015 and 2030, the number of participants in the world aged 60 years or over is projected to grow by 56%, from 901 million to 1.4 billion, and by 2050, the global population of older persons is projected to more than double, reaching nearly 2.1 billion. Globally, the number of participants aged 80 years or over, i.e., the "oldest-old" persons, is growing even faster than the number of older participants overall. Projections indicate that by 2050, participants over 80 will number 434 million, which has more than tripled since 2015 (when there were 125 million participants over age 80) [1].

Medical advances have led to this welcome increase in life expectancy. However, life expectancy has increased by more years than healthy life expectancy and therefore the number of years lived in poor health have also increased [2]. As such, new medical advances are working towards continuing to ensure that more years are spent in good health.

Osteoporosis is a disease which significantly affects healthy life expectancy, causing severe pain and disability to individual sufferers. It is described by the World Health Organization (WHO) as a "progressive systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture" [3]. Estimates of the worldwide prevalence and disability associated with osteoporotic fractures suggest that the burden of the disease compared to other disease states, using DALYs as a measure, (i.e., Disability-Adjusted Life Years which utilise number

of years lost due to ill-health, disability or early death) is second only to lung conditions [4]. In Europe, osteoporosis accounts for more DALYs than many non-communicable diseases including rheumatoid arthritis, Parkinson's disease, breast cancer and prostate cancer [4].

In the UK, approximately 536,000 new fragility fractures occur each year, comprising 79,000 hip fractures, 66,000 clinically diagnosed vertebral fractures, 69,000 forearm fractures and 322,000 other fractures [5]. Such fractures are estimated to cost the National Health Service (NHS) over £4.4 billion, each year (estimated for 2010). Hip fractures account for around 50% of the total cost of fractures to the UK annually [5]. Approximately 53% of patients suffering a hip fracture can no longer live independently and 28.7% die within 12 months of the fracture. Only 54% of individuals admitted from home with a hip fracture return there within 30 days [5-8]. More than one-third of adult women and one in five men will sustain one or more fragility fractures in their lifetime [9]. For women, it is reported that the risk of hip fracture is higher than the risk of breast, ovarian and uterine cancer combined, while for men, the risk is higher than the risk for prostate cancer [10]. The risk of sustaining a fracture increases with age. This is due to decreasing bone mass, and the increased likelihood of falling among the elderly. It is estimated that the ageing of the UK population will lead to a doubling in the number of osteoporotic fractures over the next 50 years if there are no changes made to current treatment protocols [5].

Treatment options for patients with a diagnosis of osteoporosis include Bisphosphonates in tablet or injectable form, Parathyroid hormone (teriparatide) (given by injection), Hormone Replacement Therapy (HRT), Testosterone Treatment, Vitamin D or Calcium supplements [9]. However, long-term use of bisphosphonates has raised concerns in regard to atypical subtrochanteric fractures of the femur [11]. However, to address future healthcare demands research groups are heavily focused on regenerative medicine approaches (i.e., bone tissue regeneration) as a solution for long-term orthopaedic repair which could offer significant clinical and financial gains, whilst reducing trauma to the patient. Therapeutic approaches using Mesenchymal Stem Cells (MSCs) are currently under investigation for several conditions including stroke, multiple sclerosis and diabetes amongst many others [12,13]. In recent years, exploration in the use of MSCs for orthopaedic applications has increased dramatically [14].

Orthobiologic therapy is a rapidly advancing field, which utilises cell-based therapies and biomaterials to promote bone healing and offers exciting alternatives to traditional treatment options for improving the long-term health of patients suffering from disabling musculoskeletal disorders [14,15]. Although human MSCs in bone marrow are known to decrease with age, MSCs can be expanded under culture conditions and expanded MSCs from older patients can retain effective osteogenic differentiation capacity [16]. A study by Sanghani-Kerai et al., explored the difference of characteristics between Mesenchymal Stem Cells (MSCs) harvested from young, adult, and ovariectomized rats and found that cells derived from osteopenic rats demonstrated reduced migrative capacity to stromal cell-derived factor 1. It was suggested that poor bone formation in postmenopausal women could be due to poor retention and function of mesenchymal stem cells resulting in delayed unions [17].

Although the stem cell source (i.e., autologous vs allogeneic) for these applications both have advantages and disadvantages, it is suggested that treatment decisions should be based on the age of the patient. For example, the allogeneic stem cell route would be the preferred choice for the very elderly patients, due to the fact that the quantity and quality of autologous stem cells from these patients would be very low, which would not justify inflicting further trauma to the patient by conducting an iliac crest aspiration. However, allogeneic cell-based therapies come with a view that they may elicit an immune reaction.

The use of stem cells for cell-based therapies is currently an exciting, promising and growing area for disease treatment and regenerative medicine. Furthermore, the ability to develop unique biomaterials which could harness the cells potential would also offer significant therapeutic potential. Recent Studies have shown that synthetic materials can not only influence but can also induce, lineage-specific stem cell differentiation. Studies have shown that ions (such as calcium, magnesium and strontium etc.) if released from dissolving inorganic minerals at the desired rates could influence stem cell phenotype [18]. One study showed that controlled release of calcium and phosphate ions could influence osteogenic differentiation through mechanisms involving c-Fos and adenosine signalling. Studies have also shown that it is possible to use materials to harness cell-secreted factors to amplify stem cell expansion and differentiation [18].

Public opinion on the use of stem cells in research has been well explored and remains a contentious topic globally, though research into poll trends suggests that in the US at least, an increasing proportion of the population support government funding for embryonic stem cell research and view such research as morally acceptable [19-22]. What is less well explored are the attitudes of participants towards the use of stem cells for regenerative medicine applications, particularly for therapeutic interventions amongst the older population.

A research team based at the University of Nottingham are developing an orthobiologic based material and stem cell therapy based prophylactic treatment for the prevention of fractures in participants with osteoporosis. This potential treatment could revolutionise treatments options for osteoporotic patients, especially for those considered to be at high risk of bone fracture [23,24].

However, patient perspectives on stem cell therapy related treatment options for this group of participants have not been explored before. This Patient and Public Involvement study was therefore established to explore patient perspectives of the orthobiologic technology proposed and to ascertain patient perceptions on the use of stem cells for the fracture prevention bone regeneration treatment proposed.

Materials and Methods

Design and Distribution of Questionnaires

An online questionnaire (Q1) for participants affected by osteoporosis was designed using the 'Bristol Online Survey' tool and piloted by members of the study's Patient and Public Involvement Reference Group to ensure it would be acceptable and understandable to the target audience. A postal version of the questionnaire was also available in addition to the electronic version of the questionnaire in order to address potential internet access issues likely to be experienced by the demographic of the target audience. Participants were also given the option of contacting the research team to request a paper version.

A link to the questionnaire was also promoted by the Royal Osteoporosis Society (ROS - formerly known as the National Osteoporosis Society) via its regular communication channels. In addition, a significant number of paper versions were distributed via the ROS regional groups. A link to the questionnaire was also distributed to members of an existing patient group at the University of Birmingham known as the 1,000 Elders Group.

Piloting of the questionnaire through the Reference Group took place during December 2016. The Questionnaire was launched on 13th Feb 2017 and remained open until 26th May 2017.

The questionnaire comprised of 22 questions in total with the opportunity for participants to provide free text comments on the reasons for their responses to specific questions. Participants were advised it would take approximately 20 minutes to complete. A cover sheet provided outline information on the study whilst explanatory text throughout the questionnaire provided more detailed information on specific aspects of the proposed treatment. The questionnaire comprised of five sections as follows:

- Background information on the participants' experience of osteoporosis
- Participants' opinions on the acceptability of the proposed treatment
- Participants' opinions on the anticipated results and benefits of the proposed treatment
- Participants' opinions on other considerations such as the use of donor stem cells
- Demographic information.

A paper-only version of the questionnaire (Q2) was then adapted for use in outpatient clinics in University Hospital and Queen's Medical Centre, Nottingham. The format remained broadly the same as in Q1, though a number of additional questions relating to the participants' health status, were included in this version.

Focus Groups

In addition to the questionnaire, three focus groups were held to explore a number of the issues raised by the findings in more depth. The demographic results from the questionnaires indicated that less than 2% participants who had completed the questionnaire were from a non-white ethnic group, therefore participation for the focus groups was specifically targeted at members of non-white ethnic groups. An initial approach was made to a number of community groups in Birmingham, Leeds, Nottingham and Leicester. In all, eight groups were approached. These included faith groups, social groups such as lunch clubs and groups working with local communities to support health and education activities.

The data from these focus groups were analysed thematically and the findings are presented separately to the quantitative data generated from the initial questionnaires

Ethical Review

The University's ethical approval process was followed for the development and distribution of the first version of the questionnaire (Q1) through the ROS and 1,000 Elders Group and for the carrying out of the focus groups as these activities did not involve NHS patients in NHS settings. The distribution of the second version of the questionnaire (Q2) required full HRA ethical approval, as this component of the study involved NHS patients in NHS settings.

Data Analysis

The questionnaire was designed using the Bristol Online Survey tool which includes an analytical function to derive simple descriptive statistics.

A thematic analysis of the qualitative data generated from the focus groups and free text responses to the questionnaire were subsequently carried out, guided by the principles of Ritchie and Spencer's (1994) Framework Approach [25]. This involves the initial identification of analytical themes derived from the research questions, to which additional themes can be added as new insights emerge from the data.

Results

Demographic Responses

In total, 421 responses were received from the questionnaires - 391 from Q1 and 30 from Q2. For Q1, 62% of participants reported having an official diagnosis of osteoporosis, whilst all participants from Q2 had an official diagnosis of osteoporosis, as would be expected from the

distribution mechanism. 91% of participants across both questionnaire versions were female. A good range of ages were represented by participants to both surveys (Fig. 1), though the age profiles differed slightly in that participants to Q1 had a slightly younger profile (42% of participants were below 60), whilst participants to Q2 had a slightly older age profile (43% of participants were aged over 70).

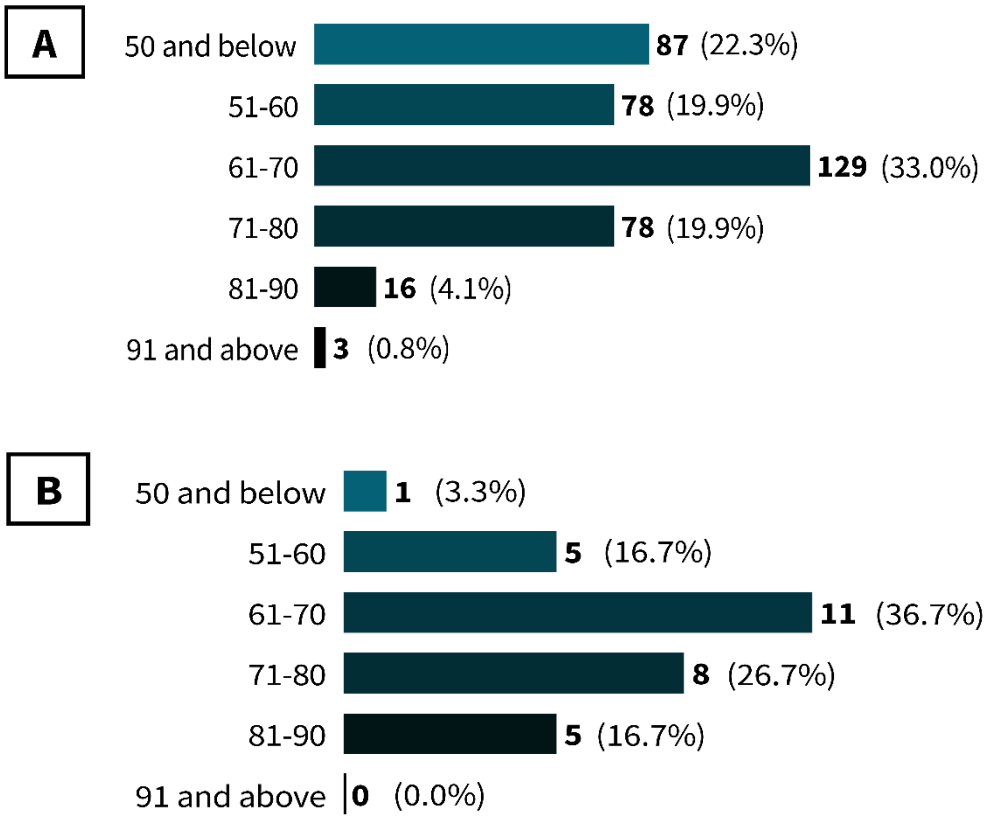

Figure 1: A) Age range of participants to questions 1 and B) Age range of participants to Q2.

Experience of Osteoporosis and Current Treatments

There was almost equal representation amongst questionnaire participants between those diagnosed with osteoporosis within the last five years and those who had lived with a diagnosis of osteoporosis for more than five years (Fig. 2). The most common form of treatment for those with osteoporosis, was Vitamin D and Calcium supplements, with 47% and 40% of participants respectively taking these supplements. The next most common form of treatment was Bisphosphonate (drug) tablets, with 24% of participants taking these. The least common form of treatment was the Selective Oestrogen Receptor Modulator (SERM) with only two participants taking this treatment.

Free text responses in the questionnaires demonstrated that many participants were experiencing distressing side effects from their treatments and many were highly doubtful of its effectiveness. Many comments were provided that suggested individuals were highly enthusiastic for development of new treatments options.

Just over half of participants with osteoporosis (52%) had a fracture due to osteoporosis. Of those, 6% of fractures experienced were hip fractures, whilst 31% of fractures reported were spinal and 28% were wrist fractures.

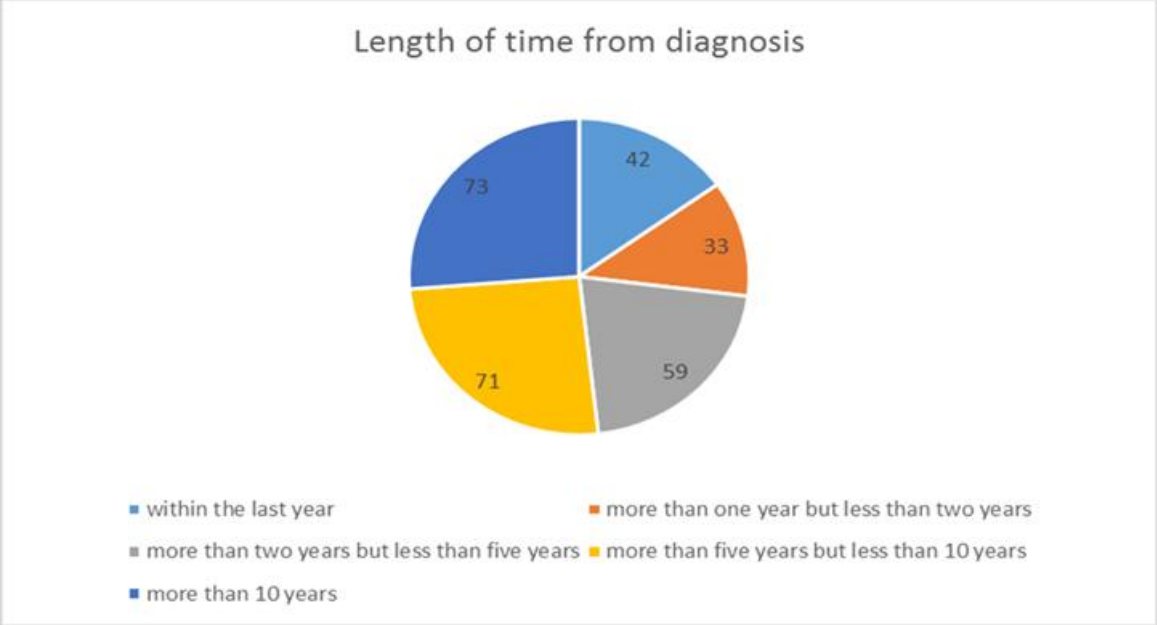

Figure 2: Participants responses based on length of time from diagnosis.

Acceptability of Treatment Responses

Results regarding the acceptability of the proposed screening mechanisms and future treatment were positive. 94% of participants to Q1 were prepared to have a DEXA scan to assess eligibility for the treatment (this question related to participants to Q1 only, as the same question was not asked of participants to Q2, as it was assumed that most of these participants would have already had a DEXA scan as part of their routine care pathway). Three-quarters of all participants (75%) were prepared to have their own bone marrow extracted for the treatment, while 73% of all participants were prepared to have more than one site treated at a time.

When disaggregating responses to the question regarding acceptability of bone marrow extraction between those participants with an osteoporosis diagnosis who had experienced a fracture and those with osteoporosis but who had not yet experienced an osteoporotic fracture, there was a trend towards the former group providing slightly more positive responses than the latter (Fig. 3). This might suggest that the experience of having an osteoporotic fracture may encourage a less risk averse attitude towards the treatment.

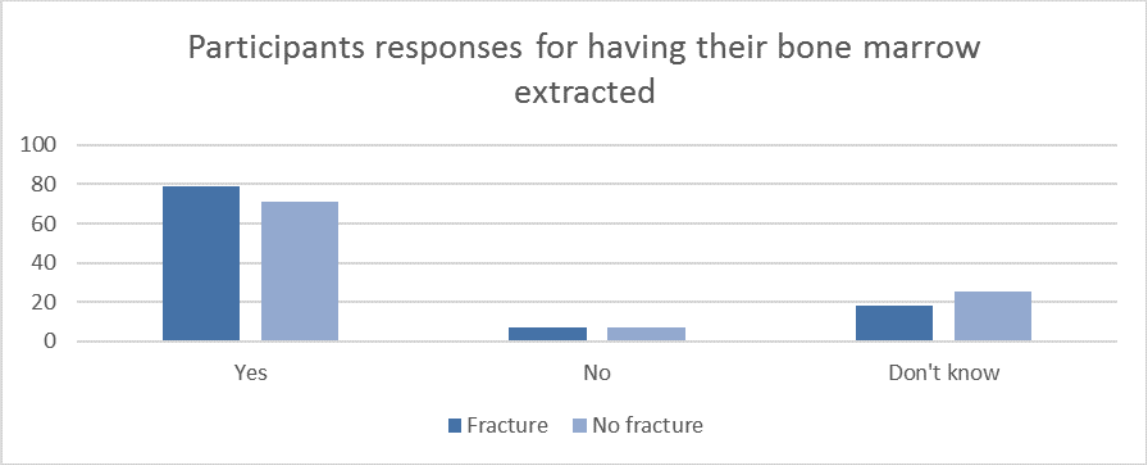

Figure 3: Bone marrow extraction split from participants who had (and had not) experienced bone fracture.

When the participants were asked about the risk of fracture reduction they would expect the new treatment to provide, 42% of all participants stated that they would accept the treatment whatever the reduction in their risk of fracture would be. Whilst 11% of participants would only accept the treatment if it reduced their risk completely. 32% of participants said that they would only accept the treatment if it reduced their risk by half. When further exploring of the answers between participants with osteoporosis who had experienced an osteoporotic fracture and those who had not, there was a slight trend for the former group to give more positive responses than the latter (Fig. 4).

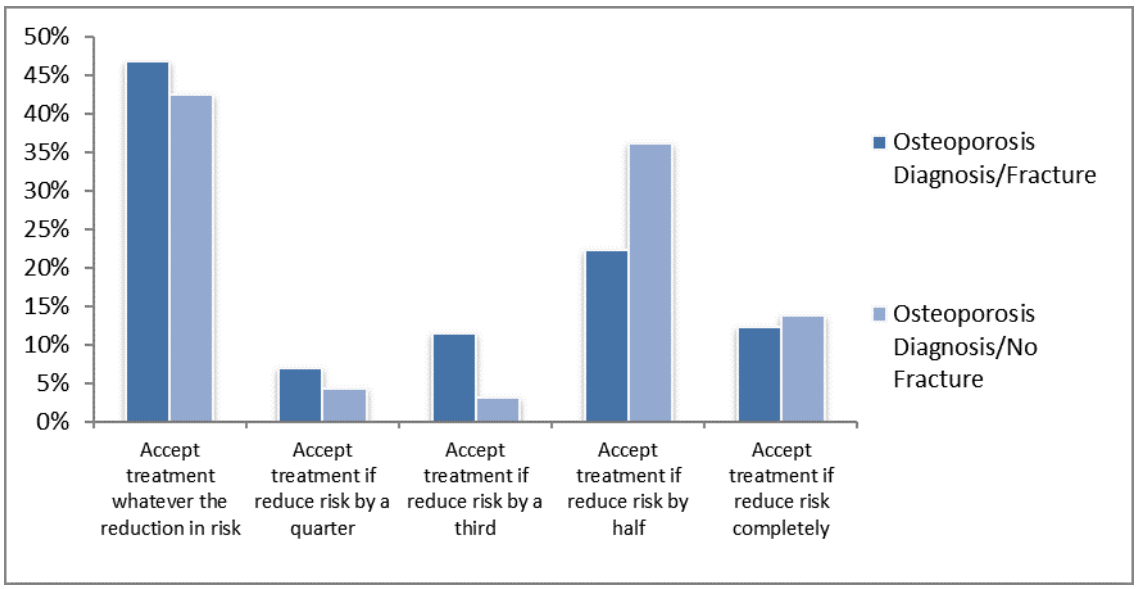

Figure 4: Responses to reduction in risk of fracture expected from the proposed treatment.

The differences highlighted in Fig. 4 may suggest a frustration with existing treatments and their efficacy, or the ability of participants to tolerate existing treatment regimes, and the desire to try something quite new different. This theme of a willingness to try anything that could make a difference was apparent in the free text responses within both versions of the questionnaire.

A high proportion of all participants (69%) stated that they would accept the proposed treatment if it reduced their risk of fracture, even if it did not improve their quality of life. For example, 73% of all participants said they would accept the proposed treatment it if reduced their risk of fracture and still required them to take their existing medication. Whilst, 68% of all participants said they would accept the proposed treatment if it reduced their risk of fracture but did not reduce pain.

Again, differences were observed in the responses between those with osteoporosis who had experienced a fracture and those with osteoporosis who had not experienced a fracture, with the former group more likely to find the treatment acceptable regardless of reduction in pain or medication and improvements in quality of life as shown (Fig. 5-7).

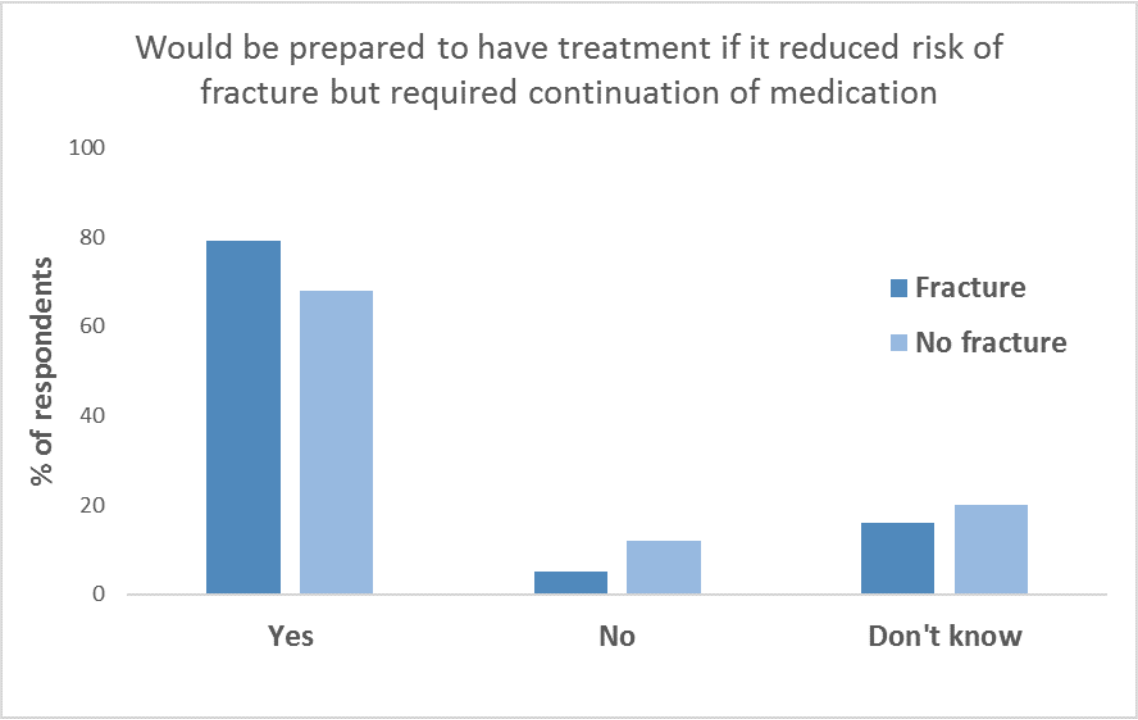

Figure 5: Response to reduction in 'Risk of Fracture' even if it did not improve quality of life.

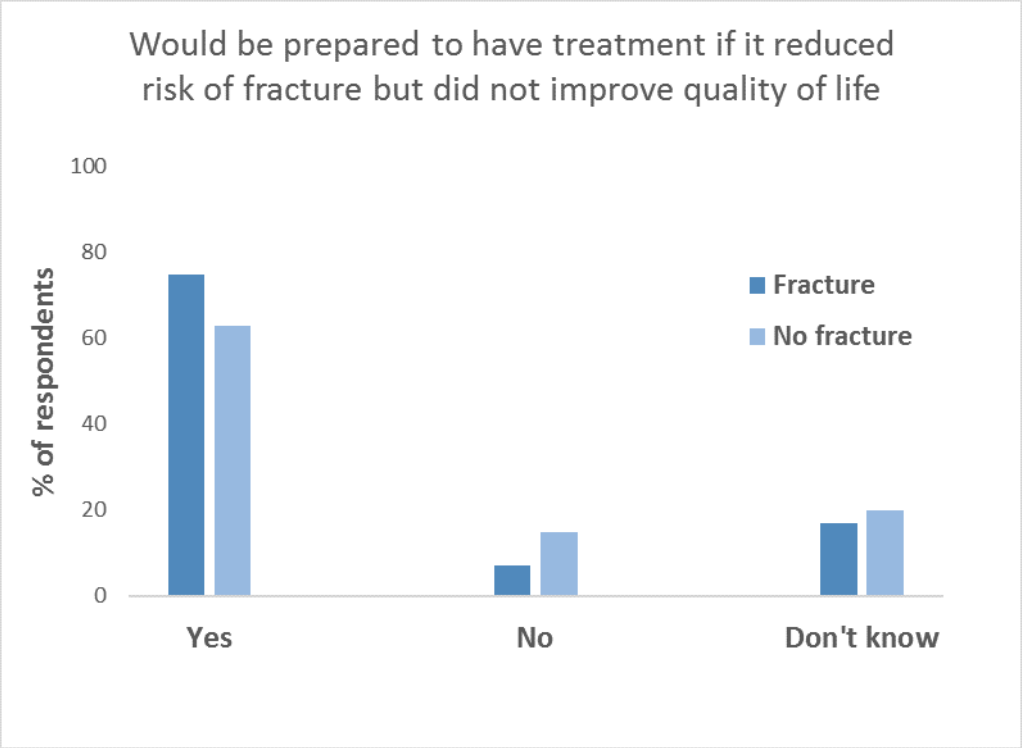

Figure 6: Participants response to reduction in 'Risk of Fracture' even if required continuation of existing medication.

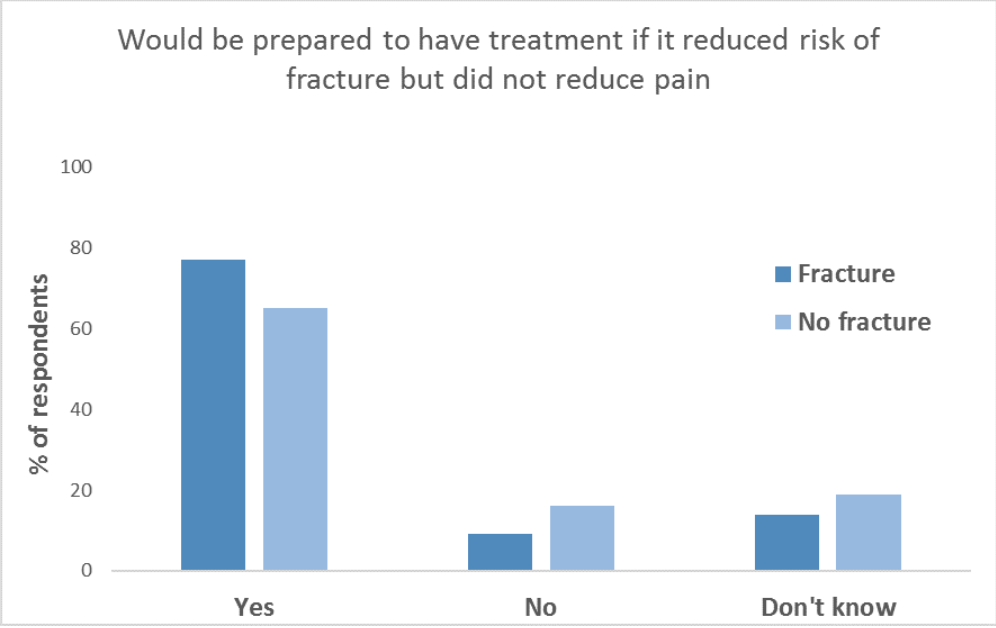

Figure 7: Participants response to reduction in 'Risk of Fracture' even without any reduction to pain.

70% of participants also stated they would be prepared to have the treatment if it required repeating once a year, with 35% of participants stating they would be prepared to have the treatment every six months, if necessary.

Findings from Focus Groups

Three focus groups were undertaken with a total of 47 participants across the three groups. Two groups were held in Birmingham:

1. With Elders having either African and/or Caribbean heritage
2. One group was held in Leicester with Elders from the Asian community. Each focus group lasted between 60-90 minutes. Of the 47 participants, only two had personal experience of osteoporosis, though others knew friends or family members who had experienced the disease.

Although the experience of having osteoporosis was limited amongst the focus group participants, the discussion within the groups raised similar themes as those raised by questionnaire participants in free text responses. These related to the nature of the biomaterial to be used, the likely effectiveness of the treatment balanced against the risk, the pain of the procedure, and the use of donor stem cells.

The idea of an injectable biomaterial treatment into their body, articulated by some focus group participants as man-made foreign objects, made a number of participants feel uneasy. A difference was articulated between having a foreign object introduced into their body for a life-saving purpose i.e., a pacemaker, and having one introduced for a purpose which might be considered to be improving quality of life, rather than saving life; with the former circumstance being more acceptable than the latter.

Some focus group participants suggested that they wouldn't want to tempt fate by having a procedure which could leave them worse off than they were before. A small number of participants thought that the procedure sounded painful and expressed the opinion that they would probably only consider the proposed treatment if they were experiencing a lot of pain that was interfering with their day-to-day lives, and were therefore willing to try anything to gain some relief.

The use of stem cells in the proposed treatment also generated a good debate within the groups. Participants were aware that stem cell treatments were being used in other areas of medicine and were generally not concerned about the possibility of using donor stem cells, though some participants with stronger religious views felt that this was a more uncomfortable prospect. The possibility of the body rejecting donor stem cells was raised and it was questioned whether osteoporosis was an 'important' enough condition to risk potential clinical consequences of stem cell rejection, unlike a life-saving treatment like a heart transplant or kidney transplant. A

preference for autologous stem cells was expressed by a number of participants and if that was not feasible, the option of a familial donor was preferred over a donor that was unknown to them. No-one within the focus groups expressed the opinion that they would definitely refuse the treatment on the grounds that the stem cells would come from a donor. Some quotes from the Focus Group participants have been highlighted below:

Risk versus Benefits

'Don't know if it's worth going through all that pain unless it was proven it would work. Would it be a one-off treatment or would it have to be repeated. Worried about long term and how your body would accept the foreign body.' (Questionnaire respondent free text response).

'I think it would depend on the benefit realised. If the treatment significantly improved my quality of life/pain etc. I would be prepared to have the treatment more frequently to maintain those benefits.' (Questionnaire respondent free text response).

'The risk of fracture would need to be greatly reduced i.e., by 50% or more. I would prefer the treatment to reduce the need for medication and I would probably not undertake treatment if pain was still felt unless it greatly reduced risk of fracture.' (Questionnaire respondent free text response).

Use of Foreign Materials

'You know, because it's not as if you're transferring cells that we generate anyway, you're transferring some foreign body into your body and it just rings alarm bells for me in that sense, from a religious point of view and not just a regular point of view.' (Focus Group 1 Attendee).

'We're tampering with cells, putting cells into materials, expecting them to degrade after however many days, what happens if it doesn't? What happens if, you know, you have other issues that suddenly pop up in that area? (Focus Group 1 Attendee).

Promoting Quality of Life Rather Than Life-Saving

'I suppose it's just like if you needed another kidney and you had to have it from somebody else. It would be the same sort of reaction really. But to me is it important enough to warrant that. Kidneys, yes. Heart, yes. Breaking your bones and limiting breaking your bones, is it as important? And there are things like replacement hips and knees and whatever as a treatment, so why this? That's my reaction. Why this?' (Focus Group 1 Attendee).

Use of Autologous Stem Cells versus Donor Stem Cells

'Would be happy with stem cells from adults. Do not want any from human embryos.'(Questionnaire respondent).

'When I considered donor stem cells I immediately thought it would be better coming from my own body but having someone else go through the extraction could save my pain and discomfort!' (Questionnaire respondent).

Discussion

One limitation of this study was that the responses to both versions of the questionnaire and comments from the focus group participants represent only U.K. based patient and public perceptions for the acceptability of a stem cell therapy intervention proposed as a prophylactic bone fracture prevention treatment. Other studies have shown that attitudes and perceptions of patients from other countries (i.e., U.S.) are morally acceptable. A further limitation of this study is that the above focus groups did not include members of the Chinese community.

Three clear themes emerged from the findings of this study:

1. The general acceptability of the proposed treatment
2. Preferences between autologous versus allogenic stem cells
3. Areas of interest or concern that future trials and studies should consider

Acceptability of the Treatment

The perceptions of participants who have osteoporosis and who have experienced an osteoporotic fracture towards the proposed treatment were particularly positive, suggesting a strong level of acceptability within this target group. There was a small difference when comparing findings from this cohort of participants to findings from those participants who did not have any lived experience of osteoporosis, with the former group having a greater inclination towards accepting the treatment than the latter. This was perhaps not surprising, as it was more difficult for participants to assess how they may respond in any given circumstances when they have not experienced osteoporosis related fractures or any of the circumstances and impact it could have on their lives.

The responses from participants regarding their acceptance of the treatment regardless of the extent to which it reduced their pain, improved their quality of life, or enabled them to stop taking current medication was particularly encouraging in their level of positivity. The small differences in responses between participants who had experienced an osteoporotic fracture and those who had not were also worthy of note. Osteoporosis is sometimes referred to as a 'silent disease' as gradual bone loss and increasing fracture risk is not generally experienced as a painful process by some individuals. Many participants therefore do not start to feel pain

from their osteoporosis until they experience an osteoporotic fracture. It is therefore quite probable that having once experienced the pain of an osteoporotic fracture, participants accept that they will live with some residual pain but are very keen to avoid that pain worsening as a result of experiencing further fractures.

A number of focus group participants expressed the opinion that they would consider the proposed treatment if they were experiencing a lot of pain that was interfering with their day-to-day lives. They felt that the trade-off between the risks and potentially painful nature of the treatment and its likely benefit was worthwhile. The degree of pain that can be tolerated by participants is highly individualistic and this therefore makes an assessment of the outcome of the pain/gain decision at the individual patient level highly problematic [26].

Regarding the potentially painful nature of the procedure itself, iliac crest aspiration procedures are certainly not pain free. These procedures require good technical skills in order to obtain samples suitable for processing and for reducing the pain associated with the procedure, which if poorly handled, could result in cancellation of the procedure. Furthermore, the type and calibre of the needles used are the main variables in this technique, the selection of which would depend on the patient's age, gender and body mass index [27]. As such it is imperative that new treatments developed remain as minimally invasive as possible.

Other reservations expressed by questionnaire participants and focus group participants were regarding the injection of the biomaterial construct, expressed by some as 'man-made foreign objects' - into the body. Though the use of *in-vivo* man-made objects within medicine is relatively commonplace i.e., pacemakers, joint replacements, breast implants etc. these are nonetheless legitimate concerns which would need to be addressed with clear, transparent patient information demonstrating how the biomaterials had been subject to stringent testing against regulatory standards, to demonstrate their safety. It is also possible that there will be some greater reluctance towards the treatment from those individuals who hold particularly strong religious views.

Articulating the concept of risk to patients and helping them weigh up the pros and cons of receiving any particular treatment is a challenging exercise, specifically when it comes to a preventive rather than a curative treatment. In this case, patients would be weighing up the potential risks of having the procedure i.e., pain, adverse reactions to drugs etc., against the potential personal benefits of the proposed treatment i.e., a reduction in risk of fracture, potentially without any other benefits such as improved mobility, or a better quality of life. A number of focus group participants and questionnaire participants expressed the view that they wouldn't want to 'tempt fate' by having a procedure that may leave them worse off than they were before. These comments may reflect the fact that for some participants, osteoporosis is not manifest e.g. they have no visible signs or symptoms of the disease and feel healthy, and therefore cannot assess the proposed treatment as being of benefit.

This attitude was perhaps an indication of what is known in psychological terms as "loss aversion" [28]. This principle asserts that the impact of loss on individuals is felt more strongly than the impact of gain. If participants have osteoporosis but do not experience any symptoms

from the disease, the potential loss of being asymptomatic as a result of a painful procedure where there is always a risk of some complication occurring, however small, would be felt more keenly, than the potential benefit of reducing their later risk of an osteoporotic fracture.

Hip and vertebral fractures, in addition to their obvious morbidity, also have a significant mortality rate [29,30]. The mobility and independence for patients having suffered hip or vertebral fractures, is often greatly reduced post fracture, resulting in higher societal costs than other common causes of prolonged hospitalisation such as cardiovascular disease, due to additional factors such as sarcopenia and poor quality of life [30]. Thus, effective prevention of bone fractures is not only vital for healthy aging, but must be considered as a potential option, especially as the elderly population increased.

Preferences between Autologous versus Allogenic Stem Cells

The use of autologous stem cells combined with the orthobiologic biomaterial (calcium phosphate porous microsphere material) for the proposed treatment, was not ruled out and it was particularly encouraging that questionnaire participants and focus group participants were not generally concerned about the possibility of using donor stem cells.

The main concern from those that did express some hesitation was based on the chance of the body rejecting donor stem cells and for some osteoporosis was not considered a severe enough disease to risk potential clinical consequences of stem cell rejection, unlike heart failure or kidney failure for example. It is worth noting however that these views were expressed by participants who had no lived experience of osteoporosis and were therefore likely to be unaware of the potential consequences of the disease (i.e., the fact that more than half of patients suffering a hip fracture can no longer live independently and that over a quarter die within 12 months of the fracture) [29].

This lack of awareness regarding the potential severity of the disease also led to some comments questioning the morality of using donor stem cells (considered by participants to be a limited resource), for a ‘non-life-threatening condition’. In reality, several research groups and companies are heavily investigating (and investing) in stem-cell scale-up manufacture. According to the latest review report published by the Cell and Gene Therapy Catapult, the network of GMP cell manufacturing facilities had doubled from 11 to 22 in five years, whilst the number of clinical trials the network facilities supported, had increased by 180% over the same period, from 21 in 2012 to 59 in 2017 [31]. The general public were likely to be completely unaware of this development however and perceptions of stem cells as a limited resource are likely to continue without a deliberate effort to inform participants.

There was also an appetite among questionnaire participants and focus group participants to explore the feasibility of having familial donors for stem cell harvesting. However, the practicalities of familial donors at this early stage in the development of bio banking would need to be carefully considered as this could place additional processes within the treatment pathway [32]. Over time however, it is anticipated that bio banking facilities would enable

families to deposit stem cells for future use for a range of treatments for family members to utilise.

Future Trials and Studies

The level of knowledge regarding osteoporosis as a debilitating disease which can lead to an increased risk of mortality, is likely to be low among the general public. This was reflected in the responses of focus group participants and questionnaire participants without osteoporosis within this study. Even amongst those diagnosed with osteoporosis, the manifestation of the disease would likely affect participants' conceptions of disease severity and risk of progression. Raising greater awareness of the disease amongst the general public and patients is therefore likely to be an important element of any future study, in order to increase an appreciation of the worth of the research and to subsequently encourage participation in future clinical studies.

Whilst the proposed treatment to be developed would remain as minimally invasive as possible, the understandable concerns that participants would have regarding the potentially painful nature of the procedure, whether using autologous or allogenic stem cells, and the potential requirement for a general anaesthetic to be administered, would also need to be addressed openly. Clear, transparent patient information would help to ensure that future research participants were fully aware of the implications of their involvement. Information regarding the potential treatment should also attempt to address the ''loss aversion'' principle by setting out the risks of the treatment against the potentially significant consequences of having an osteoporotic fracture, particularly of the hip and spine.

Patient information should also clearly explain how the biomaterial had been approved for use as a medical device. It was possible that some patients who held strong religious beliefs may find the idea of a man-made material being introduced into their body in this way less palatable and this may potentially deter some patients from accepting the treatment. Though this may only affect a relatively small proportion of the population that could benefit from this treatment, it was important that healthcare professionals understood these concerns and addressed them clearly and transparently as they arose.

The practicalities of introducing familial donors into the treatment pathway during clinical studies could also be explored, in order to test the feasibility of this option in routine practice. However, clearly discussing the source of the stem cells to be used in clinical trials, would be highly advantageous and would raise greater public and patient awareness of the developments in stem-cell manufacturing. This would potentially pre-empt any concerns participants may have regarding the use of limited stem cell resources for 'non-life threatening' conditions.

Conclusion

The proposed orthobiologic (stem cell) treatment for the elderly osteoporotic population had

a high level of patient and public acceptably. 94% of questionnaire (Q1) participants were prepared to have a DEXA scan to assess eligibility for the treatment; whilst three-quarters of all questionnaire participants (75%) were prepared to have their own bone marrow extracted for the treatment; 42% of participants stated they would accept the treatment whatever the reduction in their risk of fracture, while only 11% would accept the treatment if it reduced their risk completely. A high proportion of participants (69%) stated that they would accept the proposed treatment if it reduced their risk of fracture but did not improve quality of life, while 73% of said they would accept the proposed treatment it if reduced their risk of fracture and yet still required them to take their existing medication. Also, 68% of the participants stated they would accept the proposed treatment if it reduced their risk of fracture even if there was no reduction in pain.

A few of the focus group participants did not have any experience of osteoporosis and were therefore commenting on a theoretical scenario which may have accounted for the more conservative nature of their responses. Concerns raised through the groups focused on the potential pain of the procedure, the risk of the procedure rendering the patient in a worse condition than before, and the nature of the injected material. Focus group participants generally felt they would have to be experiencing a degree of pain that was interfering with their day-to-day lives, in order to be prepared to try this kind of procedure. This was consistent with the questionnaire findings which suggested that the experience of having an osteoporotic fracture may encourage a less risk averse attitude towards the proposed treatment, perhaps as current treatments were reported as being of variable effectiveness.

The findings presented here therefore demonstrate a clear mandate to the research team and community to continue their efforts in developing new proposed treatments for fracture prevention strategies.

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