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REVIEW ARTICLE

INTRA-ARTICULAR INJECTIONS OF FRAGMENTED, AUTOLOGOUS ADIPOSE TISSUE IN TREATMENT OF PATIENTS WITH KNEE OSTEOARTHRITIS – AN OVERVIEW

DOSTAWOWE INIEKCJE Z ROZFRAGMENTOWANEJ, AUTOLOGICZNEJ TKANKI TŁUSZCZOWEJ W LECZENIU PACJENTÓW Z CHOROBĄ ZWYRODNIENIOWĄ STAWÓW KOLANOWYCH – PRZEGLĄD DOTYCHCZASOWYCH BADAŃ

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ABSTRACT

Introduction

Knee osteoarthritis (OA) is a progressive disease leading to irreversible structural changes. Treatment of knee OA is chosen on a per patient basis depending on symptom intensity and joint condition. Cellular therapy is a promising method of treatment for pain alleviation and improvement of function of knee joint affected with osteoarthritis.

Aim

The purpose of this study is to review current results of knee OA treatment with Autologous Adipose Tissue (AAT) alone and to clarify the mechanism of action of the injected cells.

Material and methods

The PubMed database were searched for studies concerning treatment of knee OA with intra- articular injections of AAT alone. Five studies were included into this research. None of which were randomized, controlled or a double blinded study.

Results

Pericytes are known to be the cells which have capacity to differentiate into multipotent Mesenchymal Stem Cells or according to Arnold Caplan, Mesenchymal Signaling Cells (MSCs). This concept has appeared about 30 years ago. Inside the joint affected with knee OA MSCs sense the microenvironment of the defected tissues and then react by secreting bioactive molecules. These molecules serve as a safety mechanism for over- aggressive immune response, what is more several in vitro studies exist which support a concept of articular cartilage regeneration with MSCs.

Conclusions

Intra- articular injections of AAT offer a possibility of hampering progression and even reversing joint degeneration. It appears to be a safe and effective method of treatment, though more stringent and robust trials are needed to establish the specifics of its effective application in knee OA management.

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STRESZCZENIE

Wstęp

Choroba zwyrodnieniowa (ChZ) stawów kolanowych to postępująca choroba prowadząca do nieodwracalnych zmian strukturalnych. Leczenie dobierane jest indywidualnie w zależności nasilenia objawów oraz stanu stawu objętego chorobą. Terapia komórkowa jest obiecującą możliwością na zmniejszenie dolegliwości bólowych i poprawę funkcji stawu kolanowego objętego procesem zwyrodnieniowym.

Cel

Celem pracy jest przegląd aktualnych wyników leczenia ChZ stawów kolanowych wyłącznie za pomocą Autologicznej Tkanki Tłuszczowej (ang. Autologous Adipose Tissue, AAT) oraz wyjaśnienie mechanizmu działania podanych komórek.

Materiał i metody

W bazie PubMed szukano artykułów dotyczących leczenia choroby zwyrodnieniowej stawów kolanowych dostawowymi iniekcjami wyłącznie z AAT. Pięć badań zostało włączone do analizy, żadne z nich nie było badaniem randomizowanym, kontrolowanym czy podwójnie zaślepioną próbą.

Wyniki

Perycyty znane są jako komórki, które mają zdolność do różnicowania się w multipotencjalne Mezenchymalne Komórki Macierzyste lub za Arnoldem Caplanem – Mezenchymalne Komórki Sygnałowe (ang. MSCs). Ten koncept pojawił się już około 30 lat temu. Wewnątrz stawu objętego procesem zwyrodnieniowym MSCs identyfikują środowisko uszkodzonej tkanki, wydzielając następnie bioaktywne cząsteczki. Cząsteczki te odpowiedzialne są za hamowanie zbyt agresywnej odpowiedzi odpornościowej. Istnieją prace, których autorzy uznają możliwość regeneracji chrząstki stawowej za pomocą MSCs.

Wnioski

Iniekcje dostawowe z AAT dają możliwość zahamowania progresji zmian zwyrodnieniowych stawów lub nawet ich odwrócenie. Ponadto jest to metoda bezpieczna, wymagająca jednak większej ilości badań w celu ustalenia usystematyzowanego sposobu zastosowania w leczeniu ChZ stawów kolanowych.

Słowa kluczowe: choroba zwyrodnieniowa stawów, kolano, autologiczna tkanka tłuszczowa, iniekcje dostawowe, mezenchymalne komórki sygnałowe

Introduction

Knee osteoarthritis (OA) is a progressive and destructive disease leading to irreversible changes such as cartilage and/or menisci lesions, osteophyte formation and subchondral bone sclerosis. It is also a major problem for affected patients. This disease occurs with persistent joint pain, swelling, limited range of motion. In general, it affects the quality of life and impedes performance of activities of daily living. In Poland 7–8 million people suffer from OA and 25% of them have changes located in knee joints (Woszczak *et al*., 2013).

That is why it is a burden for the national healthcare system and for each patient as well (Chahla and Mandelbaum, 2018; Hermann *et al.*, 2018).

Treatment of knee OA is chosen on a per patient basis depending on symptoms intensity and joint condition. Nonoperative treatment is first line recommendation along with rehabilitation program, weight loss and nonsteroidal anti-inflammatory drugs (NSAIDs). When above treatment fails, surgical intervention may be required – arthroscopic debridement or total knee arthroplasty (TKA) (Samson *et al.*, 2007; Hiligsmann *et al.*, 2013; Bartels *et al.*, 2016; Bartholdy *et al.*, 2017; Chahla and Mandelbaum, 2018; Hermann *et al.*, 2018). To preserve a joint which destruction progress towards a total knee replacement, cellular therapy may be employed as a last resort (Piontek *et al.*, 2012a, 2012b). Pericytes, which after differentiation act as Mesenchymal Stem Cells or according to Caplan, Mesenchymal Signaling Cells (MSCs) (Caplan, 2017a, 2017b), can be obtained from several tissues like bone marrow (BM) or adipose tissue. It has been proven that fat tissue is a better source of MSCs than BM, because of the higher concentration of the cells (2% vs 0.02% respectively) (Chahla and Mandelbaum, 2018).

Aim

The purpose of this study is to review current results of knee OA treatment with autologous adipose tissue (AAT) alone and to clarify the mechanism of action of the injected cells.

Material and methods

The search for relevant studies in PubMed database were conducted in January, 2020. For inclusion in this review, the research had to concern (1) treatment of knee OA (2) with intra- articular incjection of AAT alone. There were no restrictions regarding stage of knee OA and bilateral or unilateral knee OA. Finally, after selection five studies met our criteria (Michalek *et al.*, 2015; Fodor and Paulseth, 2016; Spasovski *et al.*, 2018; Hudetz *et al.*, 2019; Barfod and Blønd, 2019). Unfortunately none of them is randomized, controlled or a double blinded study.

Standard preparation process of autologous adipose tissue

The whole procedure takes place in the operating room and the patient remains under general anesthesia during obtaining of the adipose tissue (Bianchi *et al.*, 2013; Pak *et al.*, 2017; Barfod and Blønd, 2019). Firstly, two small incisions at the height of umbilicus are made, subsequently through them the Klein solution is infused to reduce bleeding. After about 10 minutes of infiltration, liposuction with thin, blunt cannula may be performed using the same portals (Bianchi *et al.*, 2013; Pak *et al.*, 2017; Nava *et al.*, 2019; Barfod and Blønd, 2019). Obtained lipoaspirate is then processed with mechanical forces with or without enzymes (e.g. collagenase) depending on chosen method. If the lipoaspirate was digested with collagenase, than centrifugation is used to wash off the enzymes from desirable tissue afterwards (Bianchi *et al.*, 2013; Bora and Majumdar, 2017; Pak *et al.*, 2017; Barfod and Blønd, 2019). Enzymatic digestion is a more time-consuming procedure, but is thought to be more efficient because of purer population of MSCs obtained (Bora and Majumdar, 2017). Nevertheless, Bianchi *et al.* (Bianchi *et al.*, 2013) has shown that combining mechanical agitation (emulsification) with filtration in Lipogems® kit may give even more concentrated product with MSCs eliminating enzymatic process, saving time and reducing cost (Bora and Majumdar, 2017). The final product, regardless of chosen method, is transferred to syringes and then injected into the affected joint.

Results

In 2019, Barfod and Blønd (2019) treated 20 patients with symptomatic knee OA (K-L I-IV) with intra-articular injection of AAT. As in study mentioned above, KOOS (Knee Osteoarthritis Outcome Score) was the only tool for evaluation of outcome. Participants

were assessed at baseline and 3, 6 and 12 months postoperatively. Authors have found statistically significant improvement in all KOOS subscales at 12 months, but only in 4 out of 5 subscales (pain, activities of daily living, sports, quality of life) this improvement was clinically significant (increase of min. 10 points). Furthermore, 15 out of 20 patients claimed, that they would undergo this procedure again. Two patients received additional operative treatment after 12 months.

Hudetz *et al.* (2019) reported a case series involving 20 patients with late stage knee OA (K-L III- IV) treated with intra-articular injection of AAT. Patient related outcome measures consisted of KOOS, Western Ontario and McMaster Universities Arthritis Index (WOMAC) and Visual Analog Scale (VAS) and were evaluated at baseline and 12 months after treatment. Three patients have been excluded from the study, as they underwent total knee arthroplasty (TKA) before follow up time. 17 participants at 1 year follow up showed statistically significant improvement in KOOS, WOMAC (The Western Ontario and McMaster Universities Arthritis Index) and VAS (Visual Analog Scale) scores. These results may stand as a promising method for the patients with late stage knee OA who want to preserve their joint or delay eventual TKA.

Fodor *et al.* (2016) have published the results of treating 6 patients (8 knee joints, K-L I-IV) with symptomatic OA with AAT. They have used WOMAC and VAS, for functional evaluation range of motion (ROM) and timed up and go test (TUG), but also the magnetic resonance imaging (MRI) to assess the participants preoperatively and postoperatively at 3 months. 1 year postoperatively patients fulfilled only WOMAC and VAS scores. Authors have found significant improvement in WOMAC and VAS after 3 months as well as after 1 year. ROM has increased in 7 out of 8 knee joints but there was no significance in general. On the other hand in TUG the patients has achieved average improvement with 2.6 s after 3 months and it was statistically significant. What was interesting, there was no changes in MRI scan in treated knee. Undoubtedly major limitation of this study is a small group of participants and lack of control group.

Spasovski *et al.* (2018) published different results in an MRI scan. In contrast to Fodor *et al.* (2016) they have found cartilage structural enhancement and significant improvement in 2D MOCART. MRI was taken before treatment and after 6 and 18 months. X-ray was also used in this study, before treatment and 3, 6, 12 and 18 months postoperatively. Authors have not found any changes in x-ray evaluation during follow up. However, this study has included 9 patients (11 knee joints, IKDC B-C), so the conclusions are very limited again.

Michalek *et al.* (2015) included 1114 patients with symptomatic knee and hip OA in grade II-III into their study, and they have been treated with intra-articular injection of AAT. Knee joints have been evaluated preoperatively and after 12.1–54.3 months (median = 17.2 months) only with KOOS. From the whole treated group in 63% of the patients at least 75% score improvement was observed, and in 91% at least a 50% score improvement was observed respectively. Authors have emphasized that higher grade of OA and obesity were associated with poorer outcomes. It is the only study to include such a large group of patients with OA treated with intra-articular injection of AAT.

Schiavone Panni *et al.* (2019) combined intra-articular injection of AAT with arthroscopic debridement. The participants were assessed pre- and postoperatively at average 15.3 month follow up with VAS and International Knee Society (IKS) knee and function scores. Patients have shown significant improvement in IKS knee, IKS function and VAS, moreover authors found that patients with VAS higher than 8 at baseline achieved greater improvement in VAS at follow up in comparison with patients with VAS below 8, 44 ± 4% and 4 ± 15% respectively.

Discussion

Intra- articular injections with AAT is a promising method which is very effective sort of treatment of patients suffering from knee OA. However, ongoing randomized controlled trials should give robust evidences to confirm this statement.

Pericytes are known to be the cells which have capacity to differentiate into multipotent MSCs, this concept has appeared about 30 years ago (Sims, 1986; Caplan, 2008, 2017a; Caplan and Correa, 2011). In vivo they are settled inside blood vessels, especially in microvessels, where they are in contact with abluminal basement membrane (Caplan and Correa, 2011; Somoza *et al.*, 2014; Caplan, 2017a). The differentiation happens when blood vessel break or get inflamed (Caplan, 2017b). Activated MSCs sense the microenvironment of the defected tissues and then react by secreting bioactive molecules (Caplan, 2008, 2017a, 2017b). These molecules serve as a safety mechanism for over- aggressive immune response (Caplan, 2008, 2017b). MSCs enhance angiogenesis and proliferation of tissue specific stem cells and at the same time inhibit formatting of scar tissue and cells apoptosis (Tang *et al.*, 2004; Parekkadan and Milwid, 2010; Lin *et al.*, 2014; Caplan, 2017b). Therefore, it may seem that MSCs do not have the capacity to differentiate into chondrocytes, but several in vitro studies exist which support a concept of articular cartilage regeneration with MSCs (Johnstone *et al.*, 1998; Halleux *et al.*, 2001; Farrington-Rock *et al.*, 2004; Mizuno *et al.*, 2008; Vinatier *et al.*, 2009; Somoza *et al.*, 2014; de Windt *et al.*, 2015; Correa *et al.*, 2018; Kim *et al.*, 2019). De Windt *et al.* (2015) have showed an in vitro study that direct cell-cell contact between MSCs and chondrocytes is the key for optimal articular cartilage regeneration. However, authors are agreed that cartilage obtained in vitro is not exactly the same tissue as natural, weight-bearing hyaline cartilage (Johnstone *et al.*, 1998; Somoza *et al.*, 2014).

It is well established that fat tissue is superior to bone marrow as a source of MSCs, but to focus only on adipose tissue- is there more MSCs in harvested adipose tissue by itself or after some processing of the tissue? Nava and Sordi *et al.* (2019) tried to answer this question. They have shown that total amount of cells in lipoaspirate is higher than in fragmented adipose tissue (after mechanical agitation in a Lipogems® kit). However, the MSCs (CD31-) are significantly more concentrated in fragmented adipose tissue than in lipoaspirate. Furthermore, in the same study (Nava *et al.*, 2019) authors were observing the anti-inflammatory effect in vitro, based on the secretory activity of lipoaspirate and fragmented adipose tissue. Measures were made on 3, 7, 14 and 28 day after adipose tissue harvesting. The results have shown a higher level of cytokines and growth factors in lipoaspirate culture in comparison with fragmented adipose tissue on day 7 which has rapidly decreased on day 14 and 28. On the other hand, the level of cytokines and growth factors in fragmented adipose tissue culture remained stable. Hence, intra-articular injections of AAT probably have a prolonged anti- inflammatory effect inside the affected joint. These results, especially the higher concentration of MSCs in fragmented adipose tissue, support a concept of initiation of pericyte differentiation during mechanical agitation of adipose tissue.

In studies analyzed above the dosage of ADSCs was not specified. Researches who took into consideration the amount of injected cells (Vangsness *et al.*, 2014; Jo *et al.*, 2014, 2017; Pers *et al.*, 2016; Song *et al.*, 2018) have shown that it may play some role in articular cartilage and even menisci regeneration. There is no single clear conclusion regarding which dosage, higher or lower, is more effective in degeneratively changed knee joint preservation. However some authors (Jo *et al.*, 2014; Pers *et al.*, 2016) have found that, the higher level of inflammation is present at baseline, the better outcome can be achieved, regardless of the dosage of ADSCs. Unfortunately this conclusion is also based on a very small sample, in both studies only 18 patients were included.

Rehabilitation program after intra-articular injection of AAT is the next undescribed subject in literature. Although immediate postoperative care like walking with crutches, partial or none weight- bearing, joint cooling or elastic belt usage are similar among authors, further rehabilitation regimen remains unclear. Continuous Passive Motion (CPM), stationary bicycle or any form of physiotherapy are not proven to be effective after such treatment.

Patient related outcome measures are mostly based on questionnaires and VAS, which limit the results only to subjective patients' evaluation. In our opinion it also needs to be extended by the extensive and multidimensional functional assessment including walking pace, standing up from the chair, climbing and descending stairs. According to our knowledge only one study has included a functional test – TUG (Fodor and Paulseth, 2016) and it is definitely not enough evidence to confidently say that this procedure objectively improves patients' performance in activities of daily living.

Authors have shown that intra- articular injection of AAT is a safe method of treatment of knee OA. The most common complications after the injection were joint effusion and pain, both improving after standard oral NSAIDs and joint cooling. Schiavone *et al.* (2019) reported that 3 patients among treated group of 52 patients developed a haematoma in abdominal region after the adipose tissue harvesting. None of the researchers reported any incident of joint infection or cancer after the injection (Pak *et al.*, 2013; Pers *et al.*, 2016; Barfod and Blønd, 2019; Hudetz *et al.*, 2019).

Conclusions

In available literature, there are only several studies which concentrated on efficacy of knee OA treatment with intra-articular injection of AAT alone. Autologous fat tisuue offers a possibility of hampering progression and even reversing joint degeneration. It appears to be a safe and effective method of treatment, though more stringent and robust trials are needed to establish the specifics of its effective application in knee OA management.

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