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Clinical studies were conducted in cooperation with Specialist Hospital in Vogelsang-Gommern (Deutsches Zentrum fur Knorpel-und Knochentransplantationen DZKKT / klinische Abteilung fur ORTHOPADIE - German Centre for Cartilage and Bones Transplantation (Clinical Orthopedics Unit).

Study (WOMAC) on the effectiveness of a product containing hyaluronic acid and chondroitin complex in the complementary treatment to arthroscopic intervention in damage of the knee joint cartilage (research translation from German)

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The following study was conducted using of a dietary supplement called DuoVital, manufactured by Gramme-Revit GmbH. DuoVital is a dietary supplement containing hyaluronic acid and chondroitin. The trade name - Duo-Vital is the trademark of the product used on Asian markets. Product HYALUTIDIN HC Aktiv is the trade name valid for the Polish market. Both products have the same chemical composition.

Introduction: Degenerations of cartilage, also those resulting from the damage to the ligaments and menisci of the knee, are not uncommon and they almost always have multifactorial causes. The functioning of the active and passive structures of the musculoskeletal system seems to play a major role in reducing ailments. Along with the possible surgical procedures, the other complementary forms of treatment are used , such as supplementation with the nutritional formulas containing hyaluronic acid and chondroitin. Thus it is essential to examine the postulated effectiveness of the complementary therapy in the treatment of pain caused by degeneration of the knee joint. This aim of the present study is to contribute to the research in this field.

Materials and methods: In order to conduct the intervention clinical research on the effectiveness of DuoVital complex containing hyaluronic acid and chondroitin as complementary therapy, the group of patients with the limitations of motor function due to the structural damage to the knee was examined. All patients underwent arthroscopy. The study was performed before and after treatment in the randomized control groups. The WOMAC pain questionnaire was used as an assessment tool. In order to compare the individual periods of study, the total points were counted using the WOMAC scale. In the following part of the assessment it was determined whether there were any significant changes of points with respect to the average values of the group.

Outcome: As a result of comparing the experimental group with the control group in all studies, the significant differences between groups were reported. The participants of the experimental group who received a dietary supplement containing hyaluronic acid and chondroitin in addition to surgical intervention , reported significantly fewer limitations of motor function after arthroscopic surgery in comparison to the participants of the control group. In the experimental group, the reduction of pain was also more effective.

Conclusion.
The conducted study has shown that in case of the trial participants of experimental group there is a statistically significant effect of a dietary supplement containing hyaluronic acid and chondroitin on pain reduction. Therefore the conclusion may be drawn that the combination of treatment in the form of arthroscopic surgery and the concurrent administration of the hyaluronic acid and chondroitin supplement gives better results in terms of pain relief than the arthroscopic surgery as the only form of treatment. The application of the above mentioned dietary supplement can thus be regarded as a legitimate complementary treatment in surgery.

Keywords.
Gonarthrosis (osteoarthritis of the knee joint), meniscus lesions, cartilage damage, arthroscopy, hyaluronic acid and chondroitin complex , complementary treatment.

Introduction and definition of the issue.

Pathological changes in the cartilage structure in the joints cause numerous ailments of the musculoskeletal system. The risk factors which contribute to the progressive damage of the cartilage matrix as a result of increased and / or uneven load during pressure and the impact of the articular surfaces are multifaceted, and they include numerous phenomena, ranging from one-sided, monotonous motion, insufficient physical activity, abnormal position of the shoulder (both induced and inter-current) through muscle imbalance and improper nutrition up to overweight and the effects of trauma [5, 7].

In addition to these exogenous factors , the endogenous factors , such as metabolic diseases and genetic dispositions also play an important role.[5]

As a result, the occurrence of degenerative joint diseases frequently leads to arthritic joint changes which , at more advanced stages (stage III and IV,) are difficult to treat and are accompanied by pain of variable degree as well as other forms of discomfort. From the orthopedic-traumatological viewpoint, the increasing development of cartilage degeneration, particularly in the area of the knee joint, can also occur as a result of damage to the ligaments and menisci [4], wherein the loose bodies of joints enhance both the mechanical wear of cartilage and the changes occurring due to degenerative joint diseases.

The degree of cartilage damage is currently a classic indicator used to select the method of medical treatment. In order to prevent greater wear of the cartilage in the area of the knee joint, the arthroscopy surgery is performed in case of meniscus damage of first and second stage and in hyaline cartilage defects in the early stage. [3 4]. In addition to the surgical treatment, the formulas containing hyaluronic acid and chondroitin applied as complementary treatment can also contribute to the alleviation of pain caused by the osteoarthritis of knee joints. [2].

However, the effects often remain only temporary . Some patients still report that products containing hyaluronic acid / chondroitin contribute to the relief of symptoms only to a limited extent, therefore there is still a need to develop efficient and long-lasting agents to reduce the above-mentioned ailments.

Participants of the study and the methods of research.

Within the clinical intervention study on the effectiveness of the new supplement containing a complex of hyaluronic acid and chondroitin called DuoVital , the possible effects on pain reduction in the case of knee pain were examined. The study took place in cooperation with the Specialist Hospital in Vogelsang - Gommern (Deutsches Zentrum fur Knorpel -und Knochentransplantationen DZKKT / klinische Abteilung fur ORTHOPADIE – the German Centre for Cartilage and Bones Transplantation / Clinical Orthopaedics Unit) . All participants were informed about the research project and they voluntarily agreed to participate in the study. In a randomized control group, all the changes of the motor function limitations of patients were recorded using a standard questionnaire WOMAC (Western Ontario and McMaster University) . This questionnaire is designed and validated specifically for patients diagnosed with osteoarthritis of the knee and hip joints in the Anglo-American language area [1].

Experimental group n=25	Age (in years) SD 40,68 ± 9,76
Control group n=25	Age (in years) SD 36,72 ± 13,32

Table 1: Age and standard deviation of the patients' data

WOMAC - Osteoarthritis index questionnaire is a standardized self-assessment method for patients diagnosed with osteoarthritis of the knee and hip joints [6, 8 , 9].
Patients were reported to have cartilage degeneration [3] of the first stage in the form of surface cracks and fissures and the softening of the cartilage, as well as the cartilage damage of the second stage and a maximum depth of lesion less than 50 % of the thickness of the cartilage layer (Table 1). In addition to the hyaline cartilage degeneration , the fibrous cartilage damage was also found. All patients underwent the arthroscopy surgery in order to smooth the cartilage, and after surgery they underwent the physiotherapy treatments . In addition, the participants of the experimental group (hereinafter called EG) received a complex of hyaluronic acid and chondroitin over a period of eight weeks, starting from the first day after the arthroscopic surgery . The participants of the control group (hereafter called CG) did not receive this formula . The comparison of the health status of the patient before and after the surgery was performed 60 days after the surgery, while the analysis of the pre-surgery status and the one during the follow-up examination was carried out 90 days after the surgery.
In order to compare the individual time periods of study, the total score of points according to the WOMAC scale was calculated. Lower average values of total score of points during the treatment indicate the positive intervention results, while an increase in the number of points suggests the deterioration of symptoms . It was followed by the attempt to determine whether there were any significant differences in the number of points in relation to the average values of the group . Thus a separate analysis of the three sets of questions (blocks A, B , C) of the WOMAC questionnaire was carried out.
As a method of statistical survey for evaluation of regularly distributed data, the t-Student test was conducted for samples capable of forming pairs. The data of irregularly distributed values were assessed using the nonparametric Mann-Whitney and Wilcoxon test . As a measure of significance (a significant value), the threshold value $p \leq 0.05$ was selected. Since a few sets of questions in the WOMAC questionnaire remained unanswered , it was not possible to take them into account in the overall assessment. For this reason, there are differences in the number of trial participants (drop outs) between sets of questions A, B an C

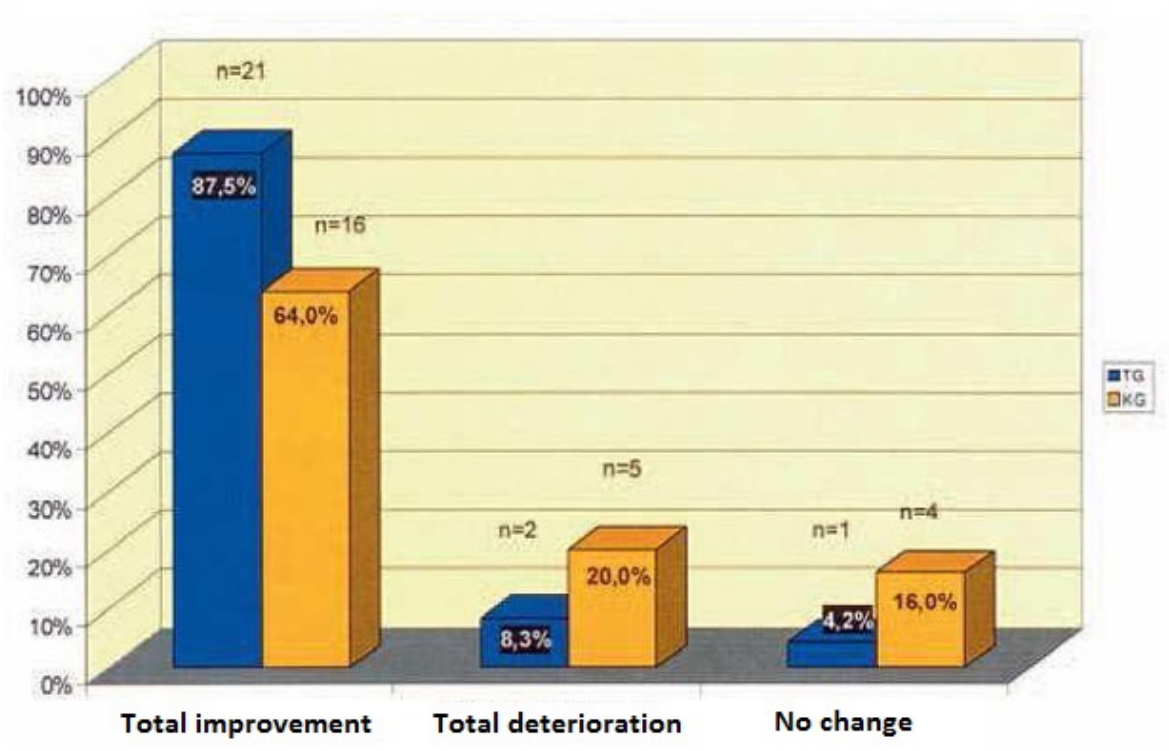

Fig. 1: Changes in the incidence of pain by the WOMAC questionnaire Part A: the comparison of pre-surgery and post--surgery medical status in control group (CG) and experimental group (EG)

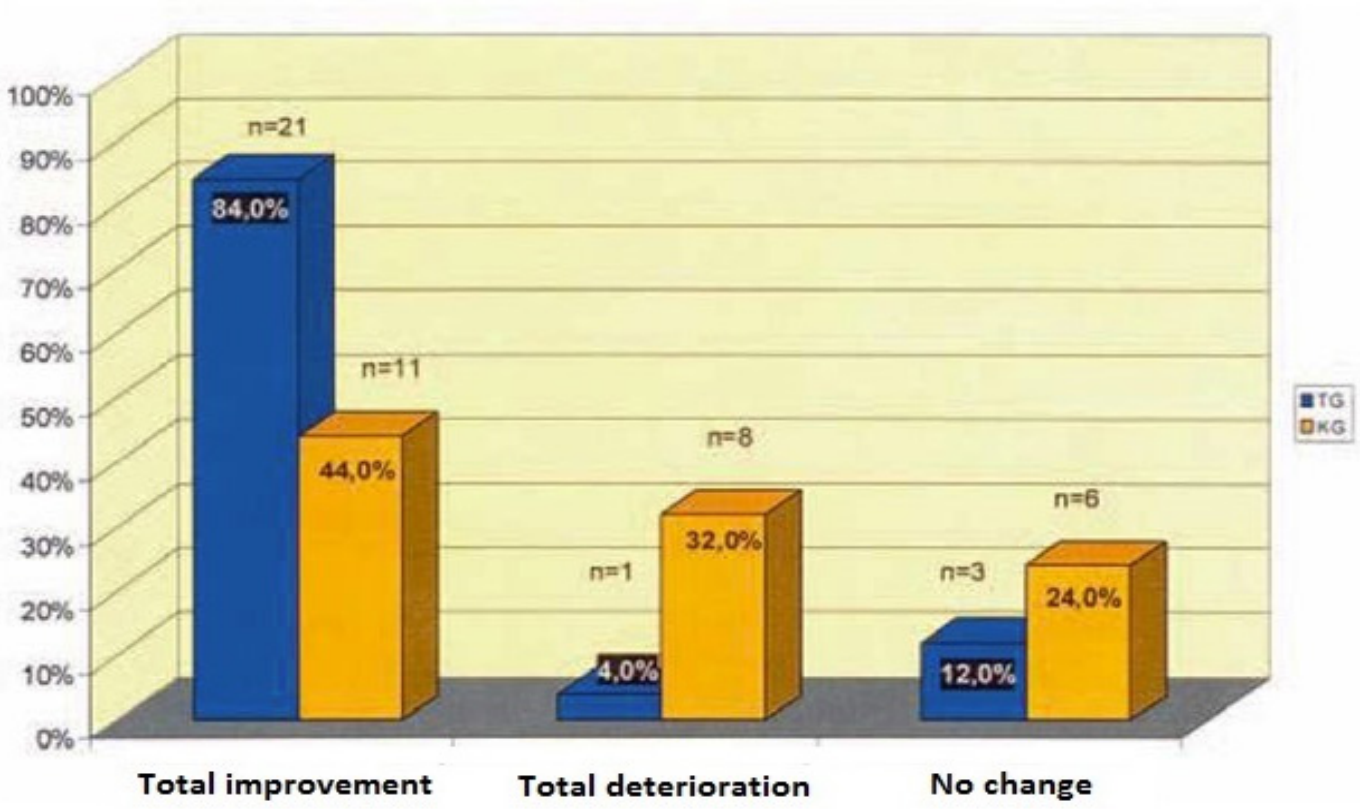

Fig. 2: Changes in the incidence of pain by the WOMAC questionnaire Part B: the comparison of pre-surgery and post--surgery medical status in control group (CG) and experimental group (EG).

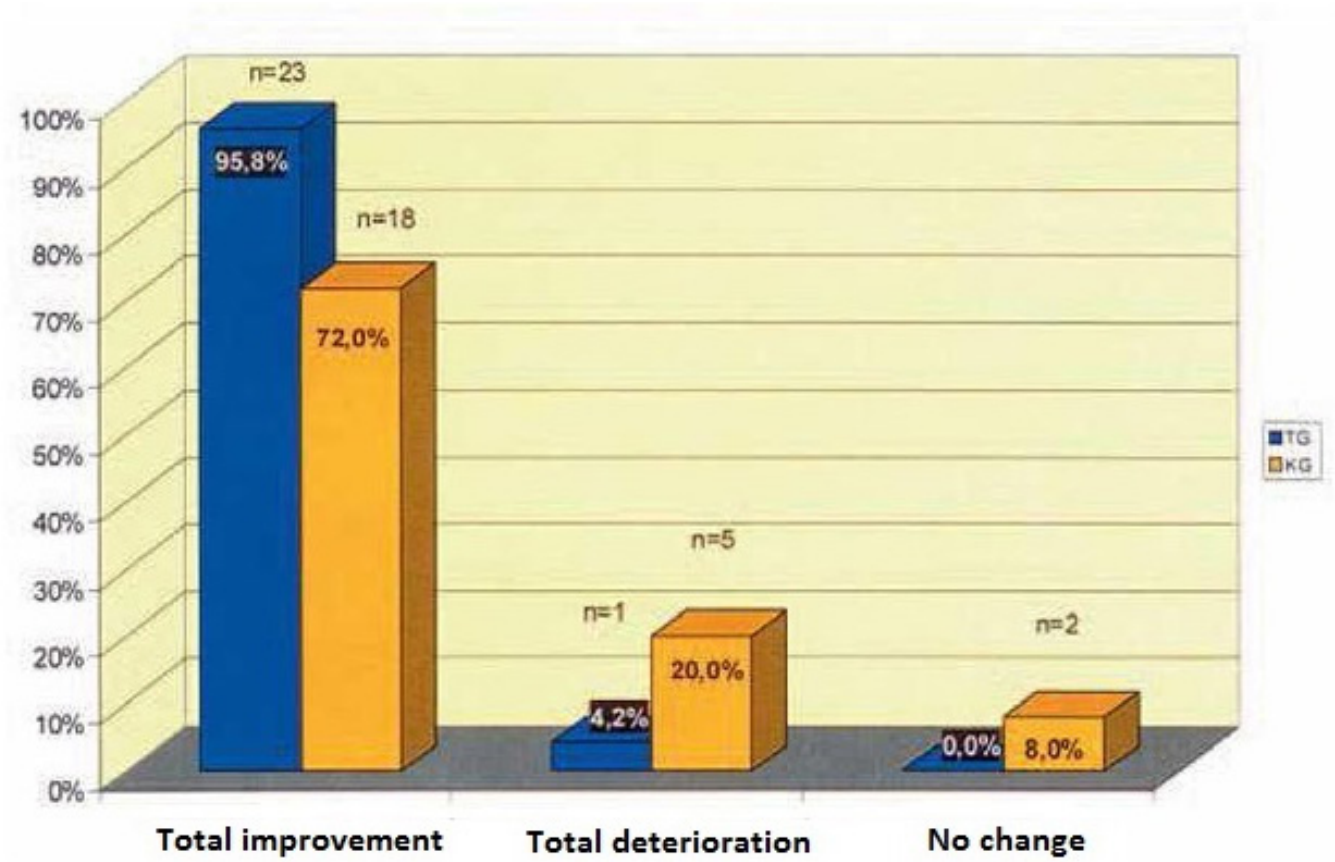

Fig. 3: Changes in the incidence of pain by the WOMAC questionnaire Part C: the comparison of pre-surgery and post--surgery medical status in control group (CG) and experimental group (EG).

Results

The results based on the WOMAC questionnaire in comparing the pre and post-surgery condition of the patient.
In part A of the WOMAC questionnaire (assessment of pain reduction) it was concluded that the general ailments occurring prior to surgery were significantly reduced after surgery in both groups. 60 days after surgery 87.5% of participants of EG reported to have fewer symptoms, or even no symptoms at all. Among the participants of the CG, the relative proportion of patients with decreased pain was 64% (Fig. 1). In both groups the reduction of the level of discomfort based on the comparison of the pre-surgery and post-surgery assessment is considered to be statistically significant (p = 0.001 - for the experimental group and p=0.036 for the control group.) The percentage proportion in reducing the level of discomfort was higher in EG (the experimental group) than in the GC (the control group)
The percentage of patients with increased symptoms according to the comparison of the pre-surgery and post-surgery medical status was higher in CG than in EG (20.0% vs. 8.3%). In addition, 16.0% of participants in the CG compared with 4.2% of EG showed no change in symptoms of pain before and 60 days after surgery. These group differences, however, could not be classified as statistically significant according to the adopted threshold value of significance (p = 0.09)
In part B of the WOMAC questionnaire (stiffness assessment), the percentage proportion of the participants who reported a reduction in symptoms (84.0%) in the experimental group (EG) was almost twice as high as that in control group (CG) , which was 44.0% (Fig. 2). Additionally, it was possible to determine that the total score of the deterioration of symptoms within the scale of points assessing the stiffness of the knee in part B of questionnaire is higher in the CG (32.0%) than in the EG (4.0%). The statistical study of changes in the mean group values indicated significant differences (p <0.001) within the group EG, whereas the difference in the pre and post-surgery state in terms of mean values within the control group (CG) were not significant (p = 0.557).
The differences between the two groups in Part B of the questionnaire were significant (p = 0.004). As a result, it could be concluded that due to the application of hyaluronic acid and chondroitin supplement within 60 days of using the formula it was possible to decrease or even entirely reduce the knee joint stiffness caused by degenerative changes or surgery in the majority of patients. The comparison of both groups in terms of Part C of WOMAC questionnaire (evaluation of discomfort occurring in physical activities of daily living) confirmed the results obtained before. In the comparison of the pre and post- surgery state, both groups showed a positive tendency, that is, the level of discomfort after surgery largely decreased, whereas the level of discomfort reduction in EG, the percentage of which was 95.8%, was once again higher than the level of discomfort reduction of symptoms in the control group (72.0%) (fig. 3).
The percentage value regarding the deterioration of symptoms in daily physical activity was higher in CG (22.0%) than in the experimental group EG , where its value was 4.2%. Considering the absolute numbers it can be concluded that, except for one participant of the experimental group , everyone else in this group was able to spend their day either without pain or with much lower level of discomfort due to combining the resection of cartilage and rehabilitation therapy with the use of a supplement containing a complex of hyaluronic acid and chondroitin . In contrast, in the control group CG, where the participant only underwent the arthroscopic surgery and rehabilitation therapy, there was a higher percentage of respondents (28.0%) in whom the symptoms remained unchanged or even partially worsened. As shown, in both groups the differences in mean group values of pre and post-surgery state were significant (p < 0.001 for EG and p= 0.008 for CG) . It may lead to the conclusion that in the participants of both the experimental group and the control group the reduction of symptoms was observed due to the use of therapeutic agents as compared to pre-surgery examination . In addition, it has been proved statistically that the relief of pain associated with physical activity was significantly higher in EG than in CG (p = 0.012) .

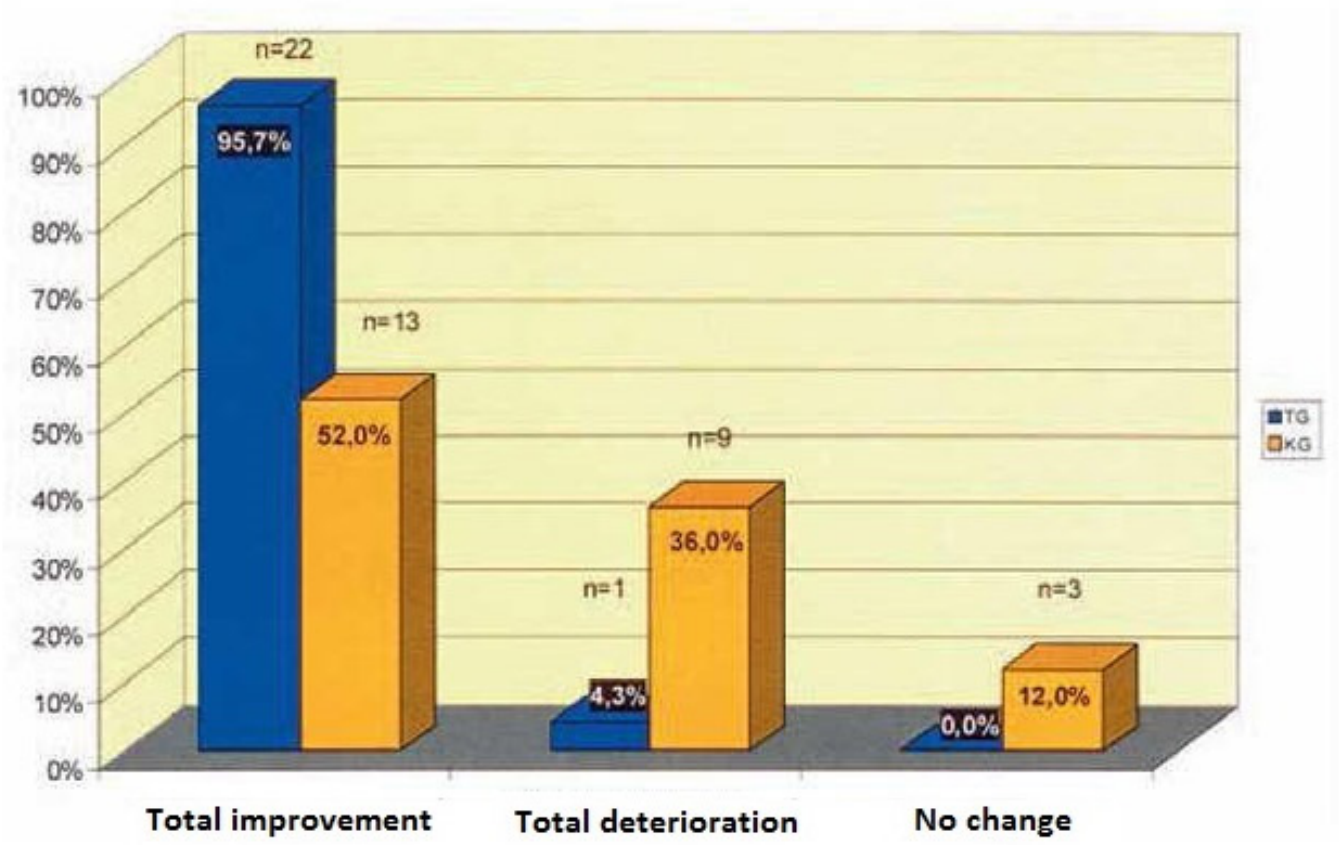

Fig. 4: Changes in the incidence of pain by the WOMAC questionnaire Part A: the comparison of the medical status during the pre-surgery and the follow-up period in control group (CG) and experimental group (EG).

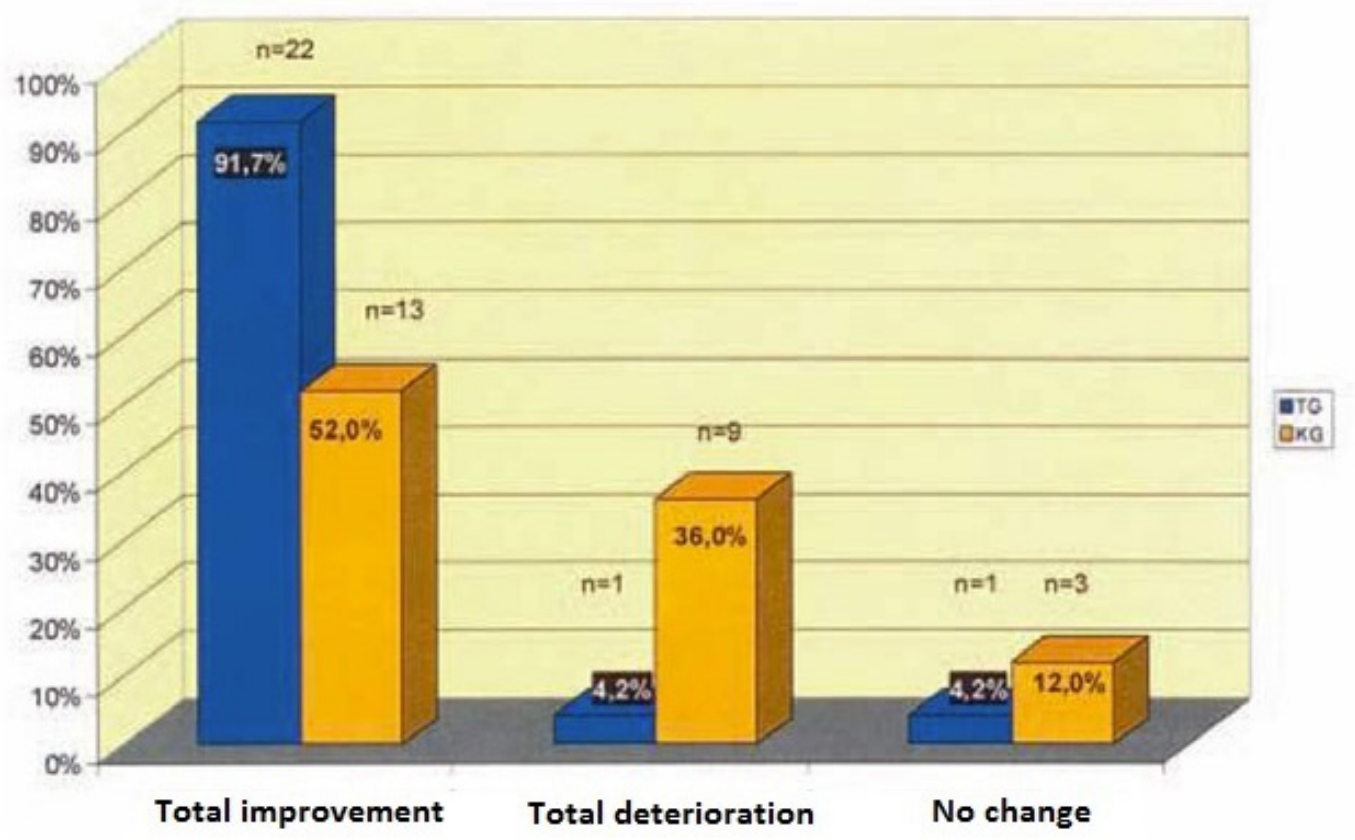

Fig. 5: Changes in the incidence of pain by the WOMAC questionnaire Part B: the comparison of the medical status during the pre-surgery and the follow-up period in control group (CG) and experimental group (EG).

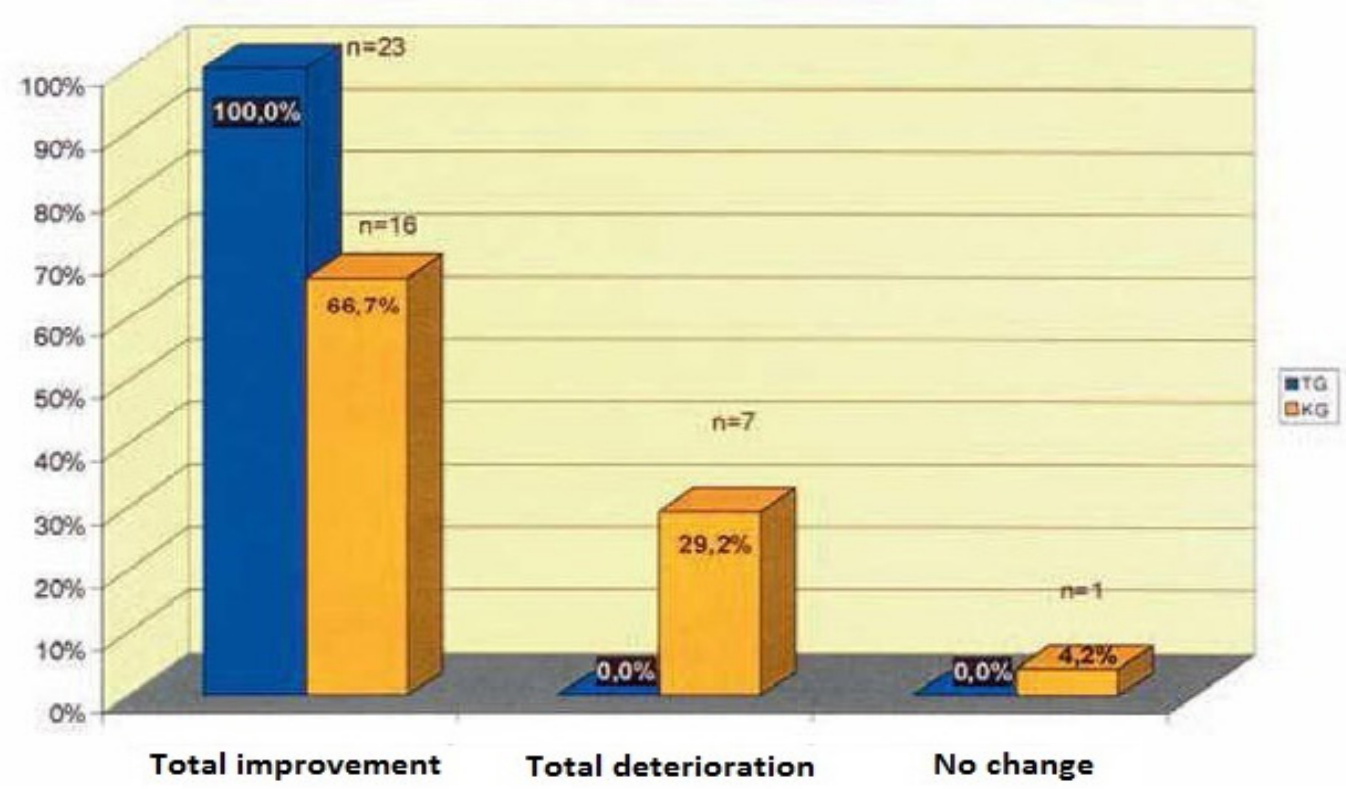

Fig. 6: Changes in the incidence of pain by the WOMAC questionnaire Part C: the comparison of the medical status during the pre-surgery and the follow-up period in control group (CG) and experimental group (EG).

The results based on the WOMAC questionnaire in the comparison of the pre-surgery state of the patient to their medical status during the follow-up examination.

In regard to a set of questions A, while comparing the pre-surgery examination and the follow-up examination it has been proved that the relative improvement amounting to 95.7% in EG has increased again 90 days after the surgery. This indicates that the level of pain was permanently lowered in patients and, additionally, the percentage of the study participants showing pain symptoms was reduced to 4.3%.
In contrast , the results of the comparison of pre -surgery state of the patients and the follow-up examination showed that in the CG group of participant the percentage of the improvement of symptoms decreased . While within the period of 60 days after surgery almost 64.0 % of the participants reported improvement in the general intensity of knee pain, 90 days after the surgery the number of positive reports decreased to 52.0 %. Simultaneously, compared to the first two studies, there was an increase in the number of participants reporting pain increase, from 20.0 to 36.0 % (Fig. 4). The changes were significant in EG ($P < 0.001$) , whereas they were not essential in the case of CG as compared to the test results within the T1 and T3 period ($p = 0.504$). The results similar to those of Part A of the questionnaire WOMAC have been demonstrated also in the comparison of the pre-surgery and follow-up examination for Part B of the questionnaire . Similarly to the general level of pain in participants in the study of control EG, the follow-up examination showed the increased percentage of participants reporting a reduction of pain symptoms associated with the knee joint stiffness in relation to the comparison of pre-surgery and post-surgery state from 84.0 % to 91.7 %, while in the CG group of patients only 52.0% reported the improvement in mobility of the knee 90 days after surgery. In addition, the percentage of relative deterioration of movement also increased in CG, thus both in B and A set of questions a high percentage of recurrences was noted. Consequently, the percentage value of the stiffness reduction in the knee joint within the control group CG was significantly lower than the percentage value in EG 90 days after the surgery(fig. 5).

As it has already been demonstrated in a comparison of pre-surgery and post-surgery state, also in case of the study comparing the pre-surgery medical status and the follow-up examination it was shown that the obtained results regarding the changes of the mean group values for the experimental group were significant ($p < 0.001$), whereas in the control group they remained insignificant ($p = 0.82$). Differences in differentiates of the total score of points in B part of WOMAC questionnaire between both groups were also considerably significant ($p < 0.001$).
In part C of the WOMAC questionnaire, the comparison of the pre-surgery examination and the follow-up examination showed that all participants of EG reported the lack of pain symptoms or their reduction after 90 days following the beginning of the experiment. Within the T2 period one of the patients of this group reported the worsening of pain. However, since one of the participants of EG was absent in T3 period, it cannot be conclusively proved whether the reduction in the level of discomfort refers to all patients because of the lack of the results of the absent patient. In the case of CG , the results of a comparison of the follow-up study and the T2 period also show better effects. Among the patients of this group, the comparison of the T2 to the T3 period of study showed that the number of participants reporting the improvement in the level of discomfort increased from 66.7% to 72%, wherein the number of patients who reported the worsening of symptoms within 90 days after surgery was lower (Fig. 6). Two participant of the study (8%) reported the lack of any noticeable changes as a result of the intervention within the period between the dates of examination. In contrast to the results of part A and B in WOMAC questionnaire, the changes in the group mean values for part C of the questionnaire were, according to the assumed level, significant in both groups ($p < 0.001$ for EG and $p = 0.012$ for CG). The differences between the two groups were also significant ($p < 0.001$).

Discussion and conclusions

The above study proves that in the case of participants who underwent the experiment there is a statistically significant effect of a product containing a complex of hyaluronic acid and chondroitin on reducing pain and discomfort. It indicates that the participants who additionally received a complex product more frequently reported the relief of pain in comparison to those in the control group As the research clearly shows, the stiffness of the knee joint in the experimental group decreased , and so did the limitations of daily physical activity , as opposed to the control group . In conclusion, it can be stated that in case of patients in middle age diagnosed with the cartilage damage of grade I – II, the combination of arthroscopic surgery and rehabilitation , followed by the administration of product containing hyaluronic acid and chondroitin contributes to the achievement of better results in terms of pain relief than in the case of treatment restricted only to arthroscopic surgery and rehabilitation .
The question of whether the study results which prove the positive effects of a dietary supplement on pain relief will be the same in case of its mono-therapeutic use to treat cartilage defects of the knee should be the subject of further studies . The issue that still remains unclear is whether the intervention combination therapy based on arthroscopic surgery and / or rehabilitation therapy and additional hyaluronic acid and chondroitin supplementation will bring the same effects in the more advanced stage of degeneration of cartilage and in case of patients of older age. This uncertainty results from the fact that the questions regarding the specific issues regarding aging and gender cannot be clearly answered on the basis of the above test results . Yet, finding the answers to these questions is of great importance since it can be assumed that degenerative changes in the cartilage of the knee are likely to increase along with the aging process. [5].
Since the importance of the issue of osteoarthritis prevention is considerably growing [4] the use of oral complex formulas containing hyaluronic acid and chondroitin characterized by high-level of bioavailability may contribute to the increased effectiveness of therapeutic and rehabilitation agents . This study was conducted with the use of a dietary supplement called DuoVital . DuoVital is a dietary supplement containing hyaluronic acid and chondroitin . DuoVital trade name has been used on the German market . Currently a product with the same composition is available under the name ArthroSedam on the German market. The distributor of dietary supplement on German market is Astellas Pharma GmbH. http://www.astellas.de/aus_der_apotheke/arthrosedam.html
Ingredients: water containing hyaluronic acid and chondroitin , invert sugar , vitamin E acetate DL -alpha- tocopherol , preservative potassium sorbate (E 202). Recommended daily dose : 30 ml for a period of 30 days.

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References:

[1] Bellamy N, Buchanan WW et al. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 1988;15(12):1833?40
[2] Bellamy N et al. The Cochrane Database of Systematic Reviews 2005; Issue 2. Z Orthop Ihre Grenzgebiete 2006;144:560?1
[3] Bös L, Ellermann A. Arthroskopische Diagnostik und Klassifi kation von Knorpelschäden. Dt. Zeitschrift für Sportmedizin 2003;54(6):123?125
[4] Höher J, Enneper J. Prophylaxe der Gonarthrose. Dt. Zeitschrift für Sportmedizin 2003;54(6):184?7
[5] Mohr W, Hesse I. Arthrose: Schicksal oder Krankheit. Internist 1998;30:633?42
[6] Roos E, Klassbo M et al. WOMAC osteoarthritis index. Reliability, validity, and responsiveness in patients with arthroscopically assessed osteoarthritis. Western Ontario and MacMaster Universities. Scand J Rheumatol 1999;28(4):210?5
[7] Steinbach K et al. Arthrose und Sport. Dt. Zeitschrift für Sportmedizin 2001; 52(3):109?12
[8] Stucki G, Meier D et al. Evaluation of a German version of WOMAC (Western Ontario and McMaster Universities) Arthrosis Index. Z Rheumatol 1996;55(1):40?9
[9] Stucki G, Sangha O et al. Comparison of the WOMAC (Western Ontario and McMaster Universities) osteoarthritis index and a self-report format of the self-administered Lequesne-Algofunctional index in patients with knee and hip osteoarthritis. Osteoarthritis, Cartilage 1998;6(2):79?86