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Comparison of Biocompatibility of Cemented *vs.* Cementless Hip Joint Endoprostheses Based on Postoperative Evaluation of Proinflammatory Cytokine Levels

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Background: The yearly increase in the number of procedures involving implantation of hip joint endoprostheses forces prosthetics manufacturers to search for biologically neutral implants. The goal of this study was to assess the concentration of Interleukin-6 (IL-6) and its correlation with C-reactive protein (CRP), depending on the type of hip joint endoprosthesis (cemented or cementless endoprosthesis) in order to determine implant biotolerance during the early postoperative period.

Material/Methods: The sample comprised 200 patients [mean age=64 (31–81) years] with coxarthrosis. All patients underwent hip joint arthroplasty using a cemented or cementless endoprosthesis. Blood samples were collected 3 times: before the procedure, on the first day after the procedure, and after 6 weeks. IL-6 and CRP levels were assayed using immunoenzymatic methods. The results were subjected to statistical analysis using the Shapiro-Wilk test.

Results: On the 1st day after the procedure, CRP and IL-6 concentration increased rapidly after implantation of both cemented and cementless endoprostheses. At 6 weeks postoperatively, the CRP value remained at a similar level in patients after cemented arthroplasty and was almost 2-fold lower in patients who underwent cementless arthroplasty. The IL-6 value returned to the baseline level in patients after cementless arthroplasty and showed an ongoing increasing tendency in patients after cemented arthroplasty.

Conclusions: 1. The measurement of C-reactive protein and Interleukin-6 is a high-sensitivity test, assessing implant biotolerance. 2. The implantation of a cemented endoprosthesis induces a higher increase in the level of proinflammatory cytokines as compared with a cementless endoprosthesis. 3. For a complete assessment of both early and later body responses to implantation and the related surgical procedure, further studies using available approaches and tools are recommended.

MeSH Keywords: **Arthroplasty, Replacement, Hip • C-Reactive Protein • Hip Prosthesis • Receptors, Interleukin-6**

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Background

The demand for total hip and knee joint arthroplasty is increasing and is expected to grow even further over the coming decades [1]. The yearly increase in the number of procedures covering implantation of hip joint endoprostheses forces prosthetics manufacturers to search for implants which will ensure optimum compatibility with adjacent human living tissues, without causing hypersensitivity reactions, which are always present after introducing a foreign object into the human body.

In case of hip joint prostheses, implantation materials implanted intratissually by means of taking over the static and dynamic functions, must not have any negative impact on the immune system, must be biologically inert, and must have the least possible effect on homeostasis [2]. Surgery is the treatment of choice in most cases of hip arthritis. Due to the rising number of hip arthroplasty surgeries performed, endoprostheses are being constantly improved. Recent papers in the relevant literature indicate a tendency to implement such endoprostheses and surgical methods that allow for optimal shifting of weight-bearing stress, similar to anatomical shifting. A successful outcome of hip joint replacement is determined by established biological fixations of implants. [3] This goal is supported by providing an appropriate integration of the implant and the osseous bed, which is to extend the biofunctional survival of the implanted elements. The implant should support bone metabolism and improve bone tissue properties, which is especial in young, active patients. Bone tissue integration to implants requires a perfect initial and ultimate stability of their junction. This stability depends, to a great extent, on the shape and geometry of the implant, as well as on its surface coating, the preliminary fitting of the implant in the patient's osseous bed, and on load distribution in the implant-bone junction [4,5]. Numerous reports have recently been published in the relevant literature, broadly covering the issues of understanding biofunctionality of different types of endoprostheses in the patient's body, assessing, among other things, the long-term outcomes of alloplastics, bone tissue remodeling around the proximal and distal parts of prosthesis stem, comparing different types of endoprostheses (e.g., cemented or cementless ones, and short or long stems), assessing the causes of prosthesis loosening after implantation, and even evaluating the quality of life in patients who underwent alloplastic [6–9]. Infection is arguably the most challenging and certainly one of the most frequent complications after joint replacement [10,11]. Clinical observations and survival analysis of joint prostheses after their implementation into the tissue clearly show that implementation of such prostheses into the tissue of a living organism often results in inflammatory processes of different intensity levels, leading to loosening of the prosthesis at the implant/connective tissue border, and the loosening process is preceded by an aseptic inflammatory reaction. Despite modern surgical prophylaxis, the incidence of this complication is rising worldwide [12,13]. Such a reaction is typical for pathophysiology of foreign bodies and is associated with biomaterials particles used for the prosthesis construction, which are released to the surroundings of the implant.

The particles released during this process induce numerous inflammatory mediators. To the best of our knowledge, the research carried out to date does not clearly state which inflammatory mediators are of key importance in the aforementioned processes. Therefore, in our study, we decided to determine the activity of interleukin 6 (IL-6) and C-reactive protein (CRP) as protein substances characterized by a variety of reactions affecting the regulation of defense mechanisms in type IV hypersensitivity reactions [14,15].

It is important to note that the present study is part of an interdisciplinary and multicenter research project carried out by the same team of researchers, aimed at multidirectional analysis and assessment of the (early and late) results of total hip joint alloplasty. The study involved: (1) postoperative evaluation of proinflammatory cytokines (Interleukin-6 and C-reactive protein); (2) evaluation of selected oxidative stress factors (e.g., TAS, and enzymes such as SOD-1, MDA, GSH-Px, and 8-iso PGF2α); and (3) evaluation of late results of the properties of bone cement, as well as the surfaces of metal and ceramic implants several years after alloplastic procedures, detected using electron microscopy and specialized biochemical tests.

The aims of this study were: (1) to estimate the concentration of IL-6 and CRP following cemented and cementless hip joint arthroplasty in order to determine the implant biotolerance, and (2) to determine if there is a correlation between serum IL-6 and CRP levels in patients who underwent cemented and cementless arthroplasty.

Material and Methods

To determine the value of IL-6 and CRP, we assessed 200 patients who underwent hip joint arthroplasty between 2010 and 2011. The patients had been operated on by the same team of surgeons at the Hospital of the Ministry of Internal Affairs and Administration with Regional Oncology Center, Department of Orthopedics Surgery, Olsztyn, Poland between January 2010 and December 2011. The sample comprised patients aged 31–81 years (mean age=64.2 years). The participants were divided by sex. One group included 126 female subjects (63%) and the other included 74 male subjects (37%).

Sample characteristics (Inclusion/Exclusion criteria): in the study described in the paper sent for publication, being the

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first part of the complex research program carried out by our team, selection of the most uniform possible sample of patients in every respect was the priority.

Patients aged 30–80 years were selected for surgical procedures (both cementless and cemented alloplastic), and the mean age of patients in both groups was similar (64.2 years). A detailed anamneses for previous conditions (mainly chronic inflammatory conditions) and a series of general medical and laboratory tests were carried out in all patients. Patients with cancer were not qualified for the study. Patients with history of chronic inflammatory conditions were excluded from the study based on the anamnesis as well as the clinical and laboratory indications. Detailed dental and laryngological examinations were carried out and, if necessary, specialist treatment was implemented at least 2 months prior to alloplasty. Each patient underwent chest X-ray and urinalysis, augmented, if necessary, by urine culture, prior to the study to assure that all patients' results were normal.

The postoperative rehabilitation protocol consisted of rehabilitation on the first day (bedside rehabilitation), and during the second day the patients were encouraged to sit up, walk, and perform active isometric exercise involving all joints.

Antibiotic treatment during the perioperative period consisted of Cefuroxime administered prior to surgery, 1 h after start of surgery, 12 h after surgery, and for the next 3 days twice daily.

Characteristics of implants (data obtained from the manufacturer) were as follow: Manufacturer, BIOMED UK LTD Europe. Taperloc I cemented implant, titanium stem, polyethylene acetabulum, metal head. Taperloc IV cementless implant, short metaphyseal stem. Press-fit titanium acetabulum, porcelain head of the prosthesis. Porcelain acetabular insert.

Composition of the metal parts of both Taperloc implants was: Aluminum 5.5%, Vanadium – DO 4.5%, Iron – 0.3%, Oxygen – 0.2%, Carbon – 0.08%, Nitrogen – 0,05%, Hydrogen – 0.015%, Titanium, and other – 90%. Polyethylene acetabula were used for cemented prostheses, made of polyethylene having a high resistance to wear and impact.

Cement characteristics were: PALACOS cement with gentamicin.

A surgeon collected blood samples 3 times: before the procedure, on the first day after the procedure, and 6 weeks after the procedure. Blood samples were analyzed in the Department of Biochemistry in Nicolaus Copernicus University, Bydgoszcz, Poland.

The material for testing was collected from the basilic vein to the test tubes with lithium heparin and to test tubes without the anticoagulant. From the blood not containing the anticoagulant (about 3 ml), serum was obtained through centrifuging the samples for 5 min at 4°C and a speed of 5000×g. Then, the serum was separated, frozen at –80°C, and stored until IL-6 concentration was determined.

Serum IL-6 concentration was determined using an immunoenzymatic method (Human IL-6 ELISA, DIALLONE, Besancon, France). IL-6 particles in the serum join anti-IL-6 monoclonal antibodies, immobilized on an ELISA plate. The free anti-IL-6, conjugated with biotin, is connected to joined IL-6 particles.

After rinsing to remove excess antibody, streptavidin HRP (horseradish peroxide) conjugate was added. HRP particles bind to the biotin-conjugated anti-IL-6. After rinsing to remove the excess of the above and adding a substrate to HRP, a colorful product was formed in an amount directly proportional to IL-6 concentration in serum, measured with the wavelength of 450 nm. IL-6 concentration was calculated using a linear calibration curve prepared with the use of standard solutions of applicable interleukin.

C-reactive protein was determined by means of a similar immunoenzymatic method using the LDN ELISA High Sensitivity kit.

Postoperative control: follow up by the end of 2012.

Statistical analysis

All the results are expressed as mean values ± standard deviation (SD). Statistical significance was checked using one-way ANOVA and the Tukey post hoc test. All p-values <0.05 were considered significant. The obtained results were subjected to statistical analysis using the Shapiro-Wilk test. The data were analyzed using Statistica 6 software.

Results

The results were subjected to statistical analysis. The mean, maximum, and minimum values were calculated for the obtained numerical values.

On the first day after the procedure, CRP concentration rapidly increased after implantation of both cemented and cementless endoprostheses. The research showed that at 6 weeks, the CRP value was maintained at levels similar to those obtained during the first day after the surgical procedure in patients who underwent cemented arthroplasty, and was almost twice as low in patients who underwent cementless arthroplasty (Table 1, Figure 1).

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Table 1. Comparison of C reactive protein CRP (mg/l) and interleukin 6 (IL-6) (pg/ml) after cemented and cementless arthroplasty (X±SD).

	Cemented arthroplasty		Cementless arthroplasty	
	CRP	IL-6	CRP	IL-6
Before the procedure	10.21±4.52	23.13±12.18	16.09±7.28	38.06±13.17
On the first day after the procedure	64.12±11.89	70.07±19.42	56.18±4.89	68.11±9.81
6 weeks after the procedure	52.26±15.32	90.11±14.21	29.15±3.21	40.04±9.62

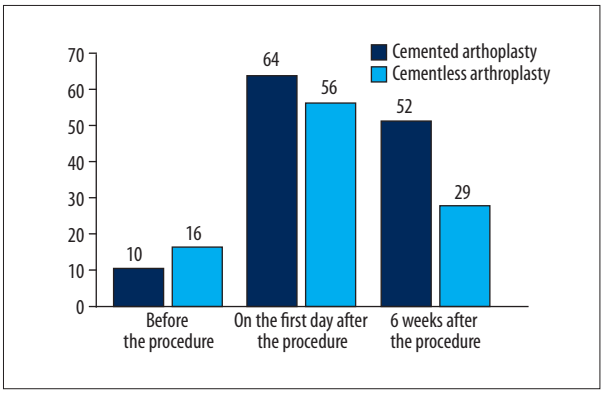

Figure 1. Comparison of C-reactive protein (CRP) after cemented and cementless arthroplasty, average values (mg/l).

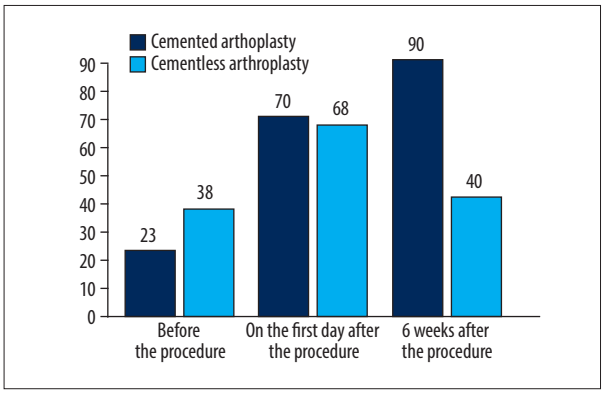

Figure 2. Comparison of interleukin 6 (IL-6) after cemented and cementless arthroplasty, average values (pg/ml).

Table 2. Comparison of interleukin 6 (IL-6) after cemented and cementless arthroplasty.

	Cemented arthroplasty	Cementless arthroplasty
Before the procedure	23	38
On the first day after the procedure	70	68
6 weeks after the procedure	90	40

The amount of IL-6 increased almost twice on the first day after the surgical procedure in both cemented and cementless endoprosthesis. At 6 weeks postoperatively it returned to the initial value in patients who underwent cementless arthroplasty, and showed an ongoing increasing tendency in patients who underwent cemented arthroplasty (Table 2, Figure 2).

The response from the human body to the implantation of a cemented endoprosthesis involves increased CRP level, proportional to interleukin 6, which is why interleukin 6 is the first to stimulate cells to produce C-reactive protein, and the values obtained during the period of clinical observations are parallel (Table 3, Figure 3).

In patients with cementless endoprostheses, a proportional increase in serum IL-6 and CRP levels was noted on the first day after the surgical procedure, after which these values decreased. After 6 weeks, the IL-6 and CRP values were similar to those recorded before the surgical procedure, as shown in Table 4 and Figure 4.

Discussion

After the implantation of a foreign body (the hip joint endoprosthesis) into the human body, a new local environment is formed and the implant may be considered to be a 'pathogen'. The implant presence stimulates monocytes and macrophages that come into contact with it, signaling the presence of a foreign body, while these cells, after being stimulated, secrete cytokines responsible for stimulation, growth, differentiation, and secretion of antibodies by B-derived lymphocytes.

CRP is a major acute-phase reactant that is produced by the liver in response to inflammation, infection, malignancy, and tissue damage [16]. Interleukin-6 (IL-6) is produced mainly by

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Table 3. Correlation of IL- 6 and CRP in case of cemented arthroplasty.

	IL-6	CRP
Before the procedure	23	10
On the first day after the procedure	70	64
6 weeks after the procedure	90	52

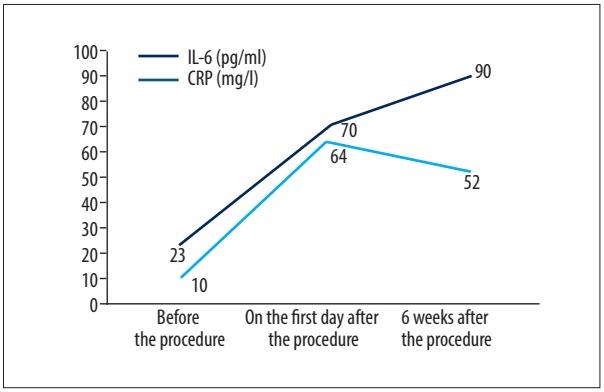

Figure 3. Correlation of IL- 6 and CRP after cemented arthroplasty.

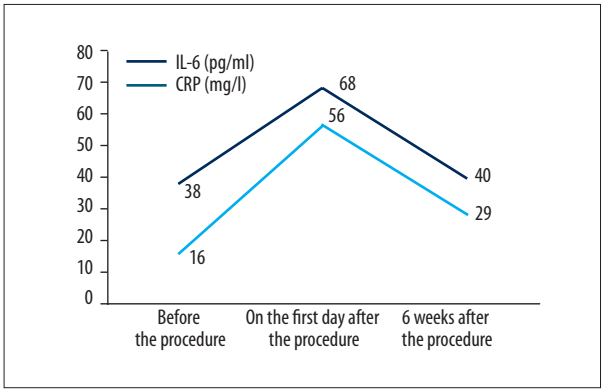

Figure 4. Correlation of IL- 6 and CRP after cementless arthroplasty.

Table 4. Correlation of IL- 6 and CRP in case of cementless arthroplasty.

	IL-6	CRP
Before the procedure	38	16
On the first day after the procedure	68	56
6 weeks after the procedure	40	29

monocytes and macrophages after antigen activation; other cells, however, such as fibroblasts, endothelial cells, and T-lymphocytes, may also synthesize it [17].

Several studies have shown that CRP levels increase within the first 48–72 h and then decrease slowly over the next several days [18,19]. Our study has confirmed this tendency. The maximum CRP levels, measured on the first day after the procedure, were found to be lower 6 weeks postoperatively after implantation of both cemented and cementless endoprostheses.

CRP and IL-6 values reflect the intensity level of immunological processes, while the main role of IL-6 is to induce the inflammatory process. Furthermore, IL-6 is principally responsible for activating CRP synthesis in the liver, which is considered the inflammatory biomarker of choice in orthopedic surgery [18,20]. CRP has been thought to be the most accurate laboratory marker [21,22].

It is assumed that after the implantation of the hip joint endoprosthesis, the process of chronic inflammatory response takes place and IL-6 influences the level of pain and the degree of tissue destruction, and causes systemic symptoms.

Our research has shown that the level of proinflammatory reaction intensity is higher after the implantation of cemented endoprostheses. The values of proinflammatory agents increase and remain at twice as high as the values obtained after cementless arthroplasty. The increase is caused by the introduction of an additional antigen (bone cement). The application of bone cement has a negative impact on implant biotolerance. Similar results were obtained in a study carried out by Zywicka [23] and Bas [24], who found that the implanted ceramic materials did not stimulate leukocytes to produce IL-6.

The amount of CRP and IL-6, determined after implantation of hip joint endoprosthesis reflect the process of potential early and late tissue reactions to implants. This is why the

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measurement of these parameters may be a sensitive test, determining biotolerance of the implant.

The above research is valuable and significant from the biomedical point of view. From the perspective of quality of life and daily functioning of patients after total hip replacement, regardless of the type of hip replacement, an appropriately designed rehabilitation program is important, and such treatment has been developed and described [25]. Our rehabilitation program takes into account carefully selected exercises in water, providing tangible benefits (e.g., reduction of pain, and improved joint mobility and muscle strength) for patients with either cemented and uncemented prostheses.

In conclusion, we emphasize again that the material used for implants was uniform and the clinical and laboratory tests used to qualify all the 200 patients for the study were uniform. Our results suggest that the cement used for alloplasty is an important element affecting CRP and IL-6 in the immune system at the early stage.

Conclusions

1. Measurement of the amount of C-reactive protein and Interleukin-6 is a sensitive test of implant biotolerance.
2. Implantation of a cemented endoprosthesis induces a higher increase in the amount of proinflammatory cytokines as compared with cementless endoprosthesis.
3. For a complete assessment of human body response to implantation and the related surgical procedure, further studies using available approaches and diagnostic tools are needed.

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