"CAROL DAVILA" UNIVERSITY OF MEDICINE AND PHARMACY

BUCHAREST

HISTOPATHOLOGIC ASPECTS OF TISSUE REACTIONS TO ORTHOPEDIC IMPLANTS

Scientific Coordinator:

Professor MARIA ARDELEANU M.D. Ph.D.

Ph.D. candidate:

CIUREA NICOLAE MARIAN M.D.

BUCHAREST – 2022

INTRODUCTION

Epidemiologic data available show that annually, in the USA, 60 million people are affected by musculoskeletal disease and traumatic injuries. This results in 1.5 million arthroplasties perfected each year in the USA, in which various types of modular prostheses are implanted, being constructed from dedicated biomaterials. Thus, every year, 645.000 knee arthroplasties, 300.000 complete hip arthroplasties, 100.000 partial hip arthroplasties, 45.000 shoulder arthroplasties and 450.000 vertebral fusion surgeries are conducted.

Having such high numbers of patients, the importance of biomaterials used in various types of implants is crucial. Prostheses fulfilling a wide range of criteria are paramount for a successful outcome for the patient.

The first requisite is biocompatibility, which means that implants need to be accepted by the patient's immune system; although some inflammation is acceptable and even desired for tissue healing, chronic inflammation is to be avoided, because it leads to septic consequences and implant deterioration.

Secondly, the implants used need to be well-constructed and sturdy, in order to resist the axial downward forces exerted by gravity and body mass (i.e. knee and hip prostheses). Meanwhile, the various subcomponents must move freely between each other, with minimal friction. In the next chapters more details about the wear and tear resulting particles (mostly polyethylene and metallic debris) will be provided. These micro particles can cause local chronic inflammation and reduced range of motion inside joints.

The surfaces of the prostheses used must be biologically stable, with no cytotoxic compounds give off in the nearby tissues.

Although the research done in this field is extensive, an ideal biomaterial that is completely inert has not been found. Moreover, some substances used in the past, in the construction of orthopedic implants have proved to be carcinogenic. In conclusion, extreme caution is needed in choosing the right type of materials for the right type of implant.

The local tissue reactions to the implant and the multiple exchanges that take place are vast and not fully understood which constitute challenging aspects while conducting research. Despite the huge number of scientific studies that describe various operative techniques of arthroplasty, only a small number of papers have been published on matters like tissue reaction to orthopedic implants.

During my practice years as an orthopedic surgeon at the Clinical Emergency Hospital in Bucharest, I have treated numerous patients with traumatic injuries which had required varied surgical interventions and ostheosynteses. Even though local progress was uneventful in most of the time, in many patients that had required implant extraction, local tissular reactions have been observed and further investigated. During tissue sampling and surgical pathology assessment, various types of inflammatory response have been signaled. This suggests that biomaterials do provoke chemical reactions and changes in the surrounding environment, resulting in an increase in complications, prolonged symptoms and even septic deterioration of the implants.

In the light of these phenomena, I decided to further investigate and present "Histopathologic aspects of tissue reactions to orthopedic implants" as my Ph.D thesis. I would like to thank Prof. Maria Ardeleanu M.D. Ph.D. for all the support offered during the development of this paper.

PERSONAL CONTRIBUTION

1. Reason for the chosen subject

Giving the fact that implant deterioration in the field of surgical orthopedics is one of the most important post op complications, which negatively impacts the mobility and health of the patient, I find it necessary to study the causes that lead to this unwanted result in a thoroughly fashion.

Although the septic development of an implant poses significant risks for the patient, that advocate for the implant removal, there are also other causes that can lead to this surgical

intervention such: uncontrolled pain, local edema without Celcian signs, loss of mobility, inability to bear weight on the affected limb (i.e. hip and knee arthroplasty). All the above represent, thus, other causes of early implant deterioration in which infection is not involved. These causes need and must be detected to further improve the functional outcome of the patients.

In the hereby paper we tried to detect and study the patient related and implant related factors that determine local complications.

The internal fixation implants and prostheses have already been extensively studied and tested in order to mask their non self signature and minimize host rejection. All that being said, there is no “perfect” biomaterial. Constant exposure to bodily fluids (blood, plasma, lymph) and tissues, determine a local response from the host’s immune system through various pathways..

If these reactions are low in intensity, no specific symptoms are reported and the wound heals properly. In this case, implant removal is not mandatory, but rather optional. The final decision is made by the patient and the doctor at a suitable time.

Otherwise, if during the healing process, pain and local swelling without signs of infection start to occur, a possible cause could be an exacerbated interaction between the implant and tissues. The treatment in this case is early removal of the implant and possibly, additional surgical interventions. Prolonging the excision surgery only increases local inflammation and tissue interaction, leading to intense bone resorption.

Other causes of implant ablation are infection, a malfunctioning implant or avascular necrosis. In the absence of the above-mentioned reactions, there are no clinical protocols in action or international consensus that guide the treatment or the right moment of excision.

Other aspects that need to be considered are patient’s age, the underlying orthopedic pathology, comorbidities, the anatomical site of intervention, possible allergies or local dermatitis, other implants or an association of biomaterials used in the construction of the same implant.

The type of implant (plate, nail, prosthesis) and the components that are part of it have also to be taken into account. Nickel, for example, alongside cobalt and chrome produce a higher

rate of metal derived allergies in comparison with other substances. The same goes for modular implants with many composing materials that create different adjoining surfaces, like in the case of hip modular prostheses (metal-polyethylene cross-link, ceramic-polyethylene cross-link, ceramic-ceramic, zirconium-polyethylene cross-link etc.). Using cement for implant fixation to the bone surface poses a higher risk for unwanted inflammatory reactions.

All that being said, we acknowledge the existence of multiple factors that can trigger these local complications, and this paper aims to recognize them, in order to lower their incidence..

2. Aims of the study

On top of what is detailed in the general part of the study, and having reviewed the existent literature on this matter, I have formulated the following hypotheses that will be tested in this study:

- Currently, there is no international consensus on how to measure local tissular reaction to a biomaterial used in surgical orthopedics;

- Simultaneously, there is no protocol that stipulates the proper moment of implant removal after a tissue reaction has been discovered; as stated before, no biomaterial has been proven to be completely inert, biologically speaking. Local interactions with the surrounding tissues is constant;

- Bearing in mind what the scientific literature has found to be true, (the persistence of implants intensifies inflammation in strength and duration and increases bone resorption and osteolysis), we reiterate the need of implant excision. However, there are no clear cut recommendations about the right moment of extraction (in case of internal fixation after trauma, there is an ongoing dispute between having to wait for bone healing or early excision, with advantages and disadvantages on both sides of the coin);

- Another conundrum is finding a reliable method of diagnosing local tissue reactions and establishing the proper time of surgical intervention after the implant has been removed.

Thus, the formulated aims of the hereby paper are as follows:

- Identifying the aggravating factors of exacerbated tissular reactions, which manifest clinically;
- Describing patient related and biomaterial related factors, in order to better formulate treatment recommendations for each patient;
- Establishing the group of patients with the highest risk of complications, caused by abnormal tissue-implant interaction;
- Characterizing inflammation and cellularity present in peri-implant tissues through pathology assessment and correlation with the corresponding symptoms;
- Finding links between patient/implant derived factors and local complications (septic, foreign body reaction);
- Histological analysis of peri-implant tissue excised during operation and quantification of foreign body reaction (acute inflammation, chronic inflammation, foreign body giants cells, fibrotic tissue).

3. Inclusion and exclusion criteria in the study

Inclusion criteria in the study:

1. All patients were over 18 years old, they were compliant, respecting medical recommendations, having presented to the imposed check-ups. All of them have signed declarations of consent in order to take part in the study;
2. All patients have undergone surgical procedures of implant fixation in the past (hip and knee prosthesis after trauma/osteoarthritis, intramedullary and paracortical implants).

3. Afterwards, all patients underwent implant removal surgery, after which macroscopic tissue inspection was performed in order to grossly quantify metallosis. Sampling for pathology assessment was also performed;
4. The surgical recommendation for implant excision was subjective (meteosensitivity, mobility loss) or objective (local edema, implant deterioration).

Exclusion criteria in the study:

1. Patients under 18 years old;
2. Non compliant patients, whose evolution could not be observed;
3. Patients who underwent non implant surgeries (sutures, tendon reinsertions, which obviously did not implied materials to be extracted);
4. Patients operated on, using absorbable materials, who had a favorable evolution. In this case, surgical intervention for tissue sampling wasn't needed.

4. Materials and methods

This research is a transversal type study and includes 68 patients, who were diagnosed and treated on the Orthopedics Ward of the Clinical Emergency Hospital in Bucharest. The cohort encompassed patients who required implant fixation surgery. Afterwards, the same patients also underwent implant excision and microscopic analysis of peri-implant tissue.

The period of time during which the study took place was 01.11.2014 - 31.12.2021. The data processing took until 31.03.2022. The number of patients observed is lower than one would expect because of the impediments caused by SARS COV 2 pandemic. Thereby, between march 2020 and january 2022 numerous restrictions on elective treatment hospital admissions were in place, which inherently lowered the number of eligible patients for the study.

The patients' variables that were considered for the study are as follows:

1. Demographic data: age, sex;
2. Patient related factors:
    - History of allergies or dermatitis;
    - The presence of other types of implants;
    - Comorbidities;
    - Symptoms: pain, pruritus, inability to bear weight, mobility dysfunction;
    - Clinical signs: local edema, skin reactions, acute inflammation signs, local pathologic secretion, hydrarthrosis, joint stiffness;
    - Radiologic signs: implant deterioration, osteolysis, non union, osteitic callus;
    - Pathology of wound healing: wound dehiscence, suture granulomas' presence;
    - Local infection;
    - Macroscopic intraoperative analysis of tissues adjoining the implant: signs of fibrosis and metallosis;
    - Histopathologic analysis of tissue samples: inflammation degree and cellularity;
3. Implant related factors:
    - Type of implant: intramedullary nail, paracortical plates, K wires, screws, tension bands, hip and knee prostheses;
    - Type of structural components of the implant: titanium alloys, stainless steel, cobalt, chrome, or alloys between these metals used in modular prostheses;
    - Type of coating: porous titanium, porous hydroxyapatite;
    - Period of time between implant fixation and implant removal surgery: less than 3 months, between 3 and 6 months, between 6 and 12 months, more than 12 months;

5. Data processing

SPSS Statistics (Statistical Product and Service Solutions) software program was used to process data for this study. This softwear is used for generating statistics in the medical field worldwide.

The cohort studied included 68 patients treated on the Orthopedics Ward of the Clinical Emergency Hospital in Bucharest.

Descriptive statistical analysis was performed in line with the set aims of the study. For the Chi-squared distribution a less than 0.05 p was employed. Additionally, $p<0.05$ was considered statistical significant, $p<0.01$ was dubbed very significant and $p<0.001$ was highly significant from a statistical perspective.

In order to test the correlation between various parameters, ANOVA test and the Bonferroni correction have been employed.

6. Results

6.1. Demographic data

To better analyze the patients' cohort, I divided it in 4 age groups. The first contains 18 to 30 year olds – 16 patients (23.52% of total), the second pertains to 31 to 50 year olds and it has assigned to it 28 patients (41.17% of total). In the third category, 51 to 70 year olds, 14 patients exist (20.58% of total). The last group contains the last 10 patients provided by the study, with ages exceeding 70 years old (14.70% of total.)

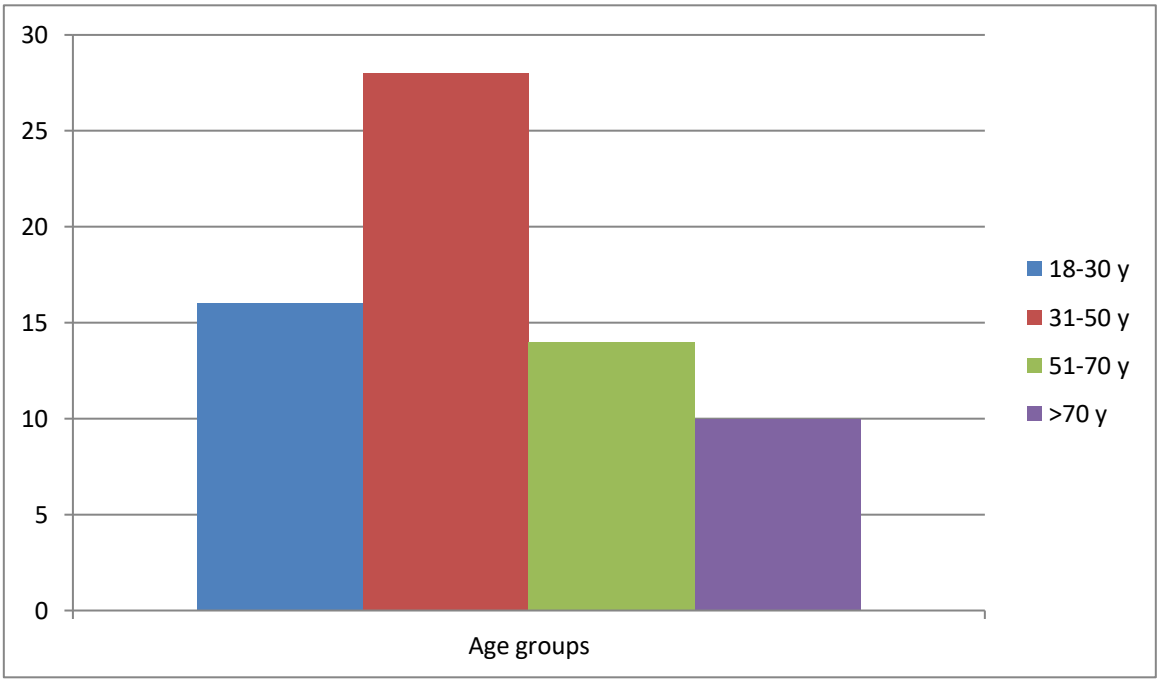

Fig. 1 Age groups

It is noticeable that younger patients tend to have higher rates of implant removal surgeries compared to older ones.

As for patients' gender, out of 68 patients enrolled in the study, we identified 43 males (63.23%) and 25 females (36.76%).

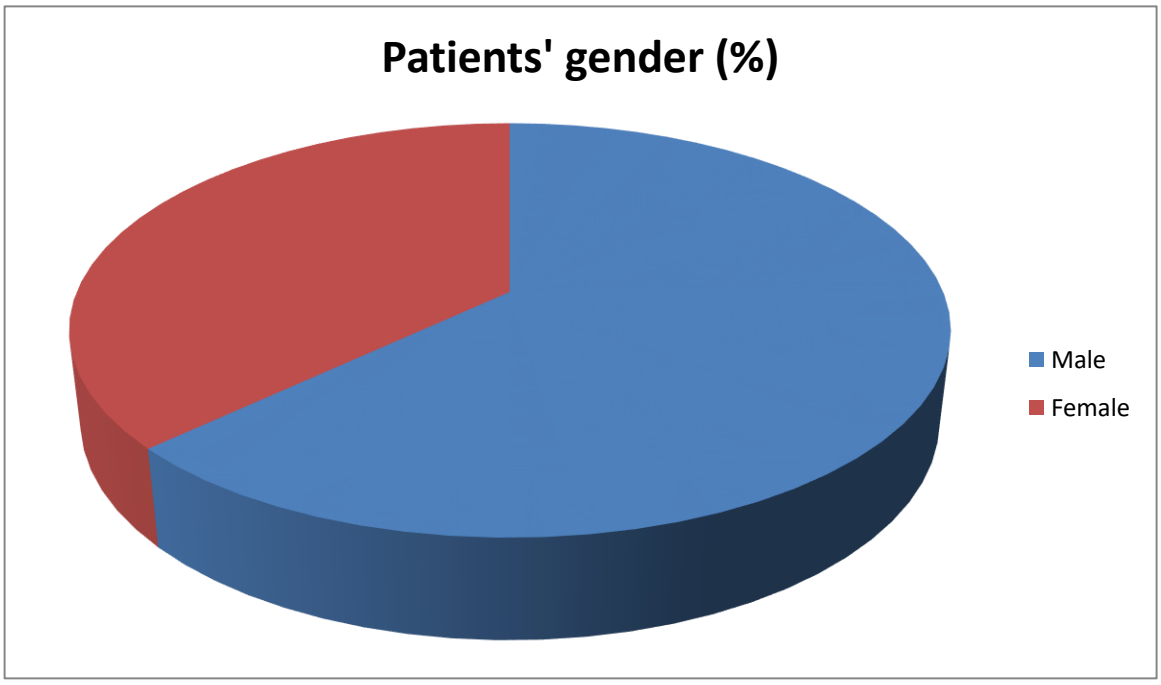

Fig. 2 Patients' gender distribution

6.2 Patient related factors

6.2.1 Personal history of dermatitis or allergies

We identified 18 patients with a history of allergic reactions or dermatitis. Out of them, 3 had contact dermatitis to metallic products (buckles, jewelry), 5 patients had allergic asthma, 3 patients experienced allergic reactions to certain foods and 7 subjects presented with allergies to certain drugs.

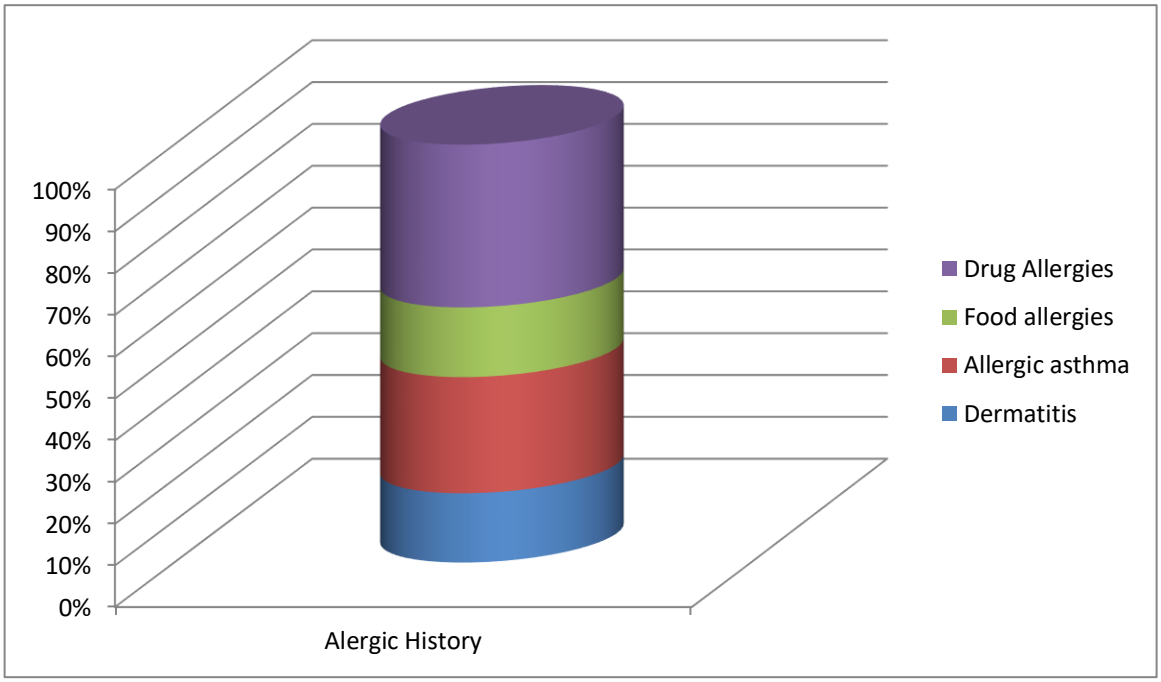

Fig. 3. Allergic History

6.2.2 Co-existent biomaterials at the time of the surgery

Out of 68 patients considered for the study, 26 had undergone surgeries in which other biomaterials were implanted, as follows: 4 patients had pacemakers, 15 patients had other internal fixation materials (4 subjects with intramedullary nails, 7 with paracortical plates and 4 patients with modular prostheses). In 7 instances cardiac stents had been implanted (3 cardiac and 4 arterial stenting cases.)

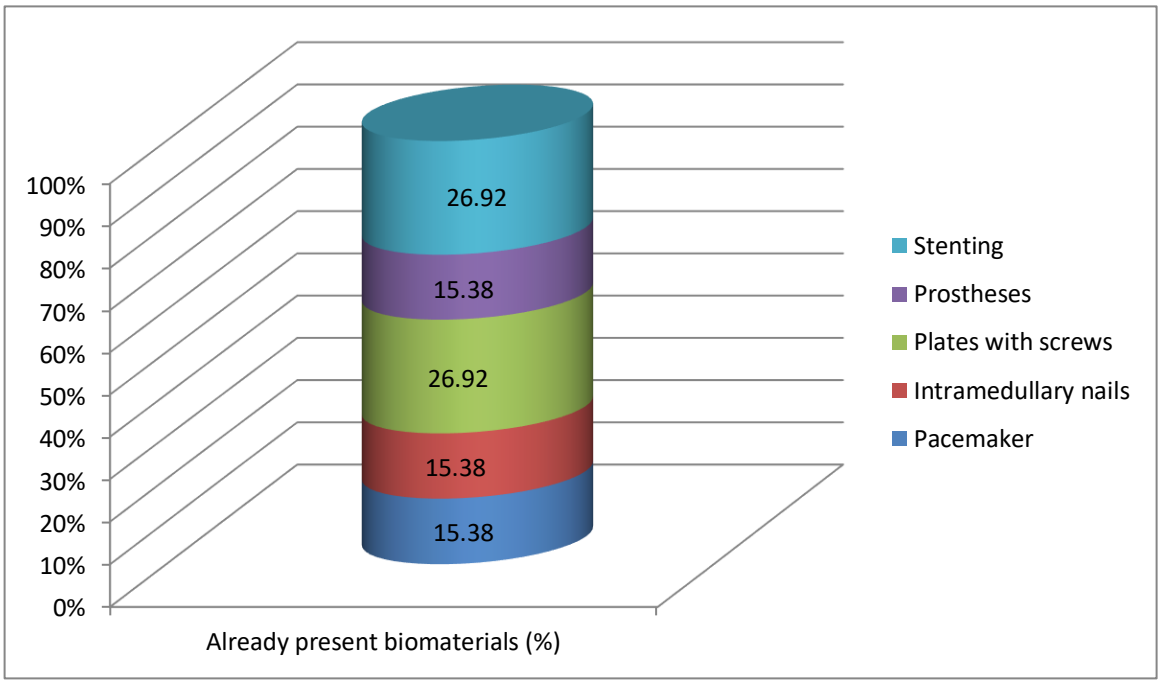

Fig. 4. Other biomaterials already present

6.2.3. Comorbidities

Among all the cases presented, 49 had long standing comorbidities. Cardiac conditions like arterial hypertension, ischemic heart disease, heart angina accounted for 44.89% of the total (22 patients). 11 patients (22.44%) had diabetes mellitus, 9 subjects suffered from neuro-cognitive disorders (18.36%), and 7 patients had a history of malignant tumors (14.28%). Out of these, 26 cases presented with 2 or more conditions of the type described.

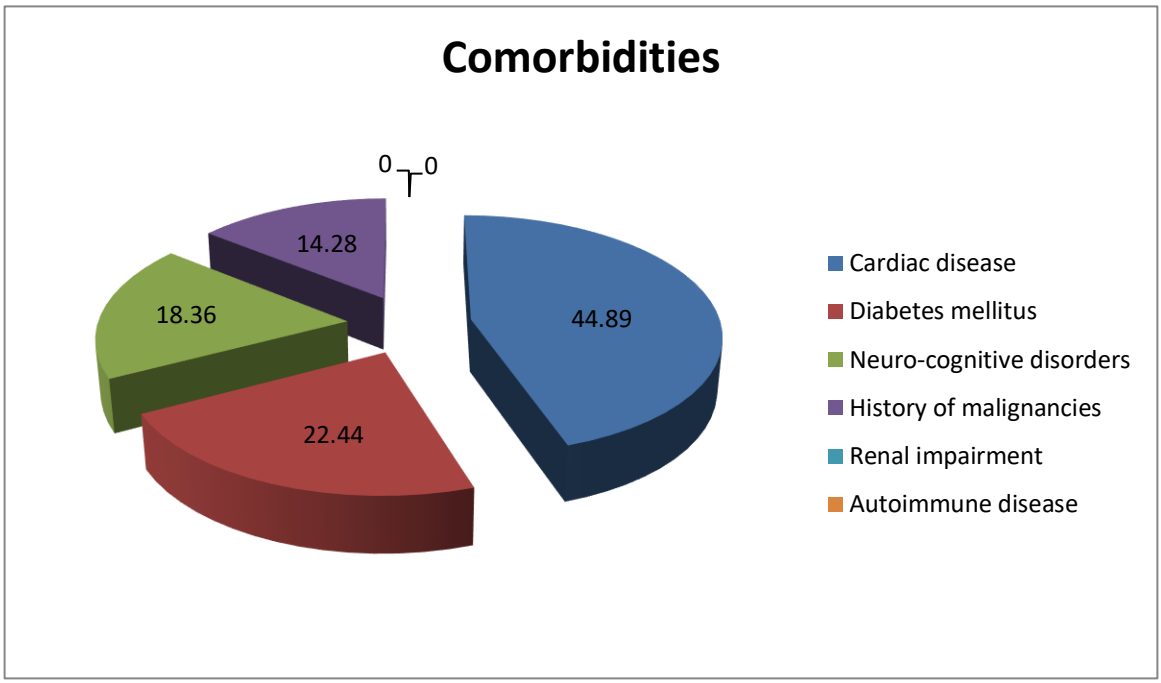

Fig. 5. Comorbidities

6.2.4 Symptoms

As for clinical symptoms, among all 48 patients we recorded the next symptoms: localized pain was the most frequent symptom (23 patients, 47.91%)., irrespective of effort or meteosensitivity. Localized pruritus affected 10 patients (20.83%). 6 subjects (12.5%) complained about inability to bear weight on the affected limb caused by skeletal instability or crippling pain. Complete loss of function in one of the limbs affected 9 patients (18.75%).

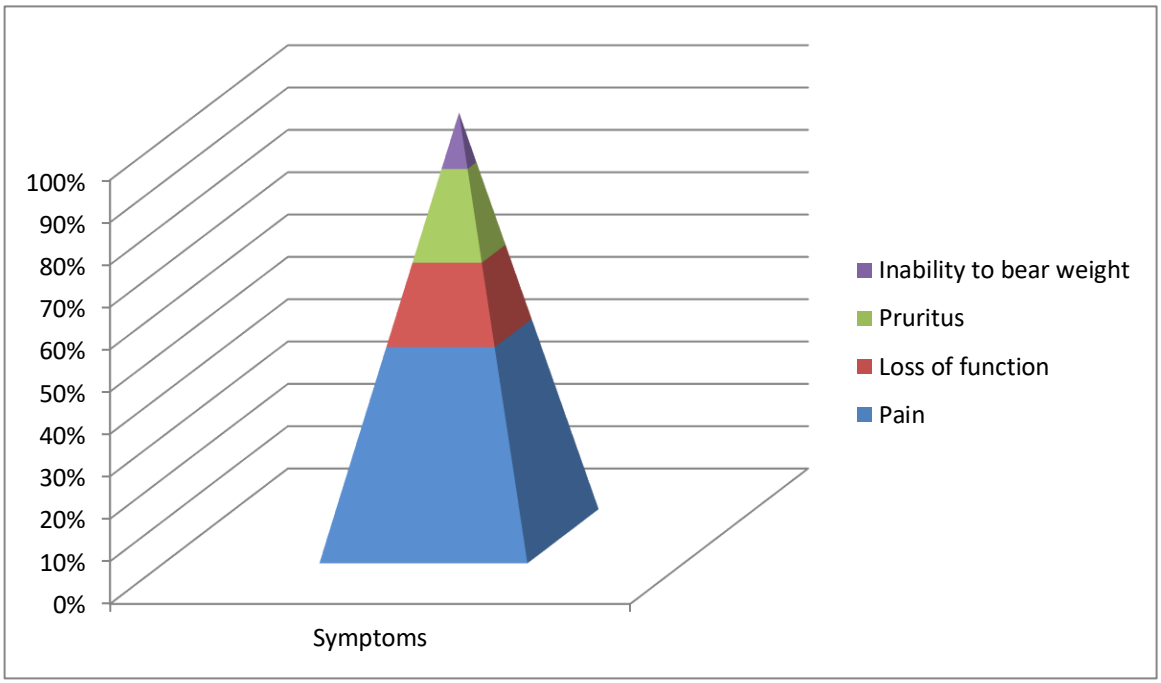

Fig. 6. Symptoms

6.2.5 Clinical exam

As for the local illness signs, we have identified: local edema in 26 patients, tegumentary reactions in 8 patients, acute inflammation in 18 cases, local pathological secretions in 12 subjects, hydrarthrosis in 5 patients and joint stiffness affecting 10 patients.

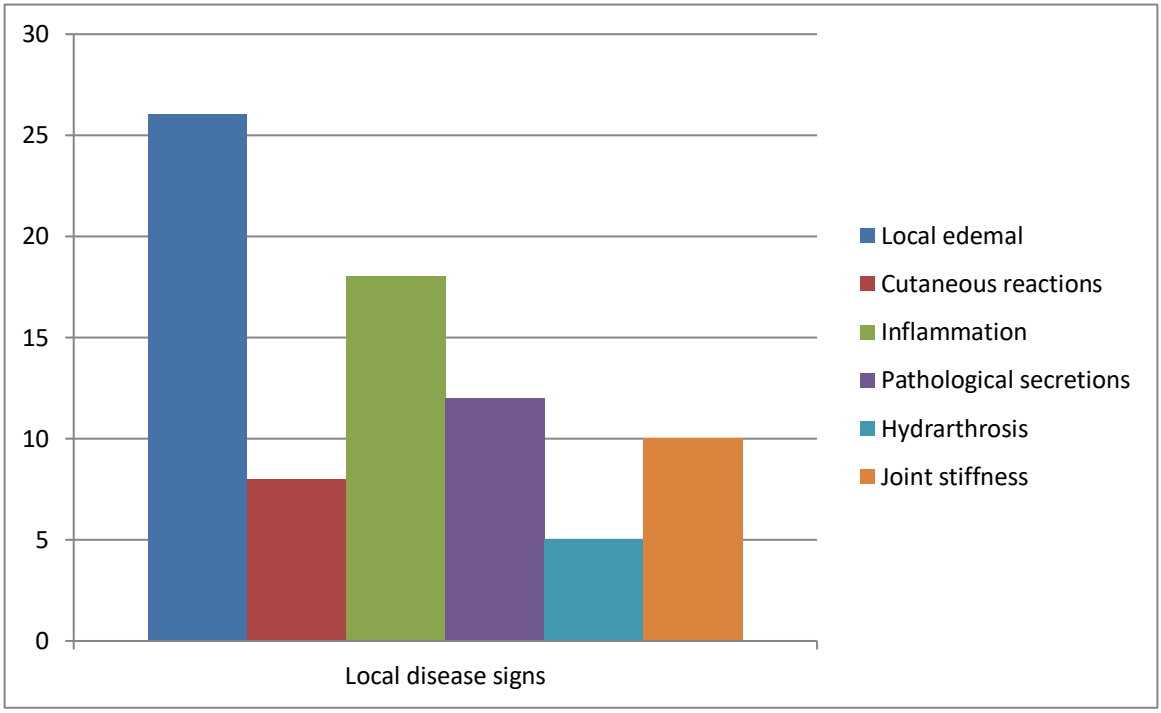

Fig. 7. Local clinical exam

6.2.6. Radiologic signs

The following radiologic signs have been described: implant deterioration or migration in 14 cases, osteolysis for 9 patients, non-union in 12 cases and osteitic callus in 4 instances.

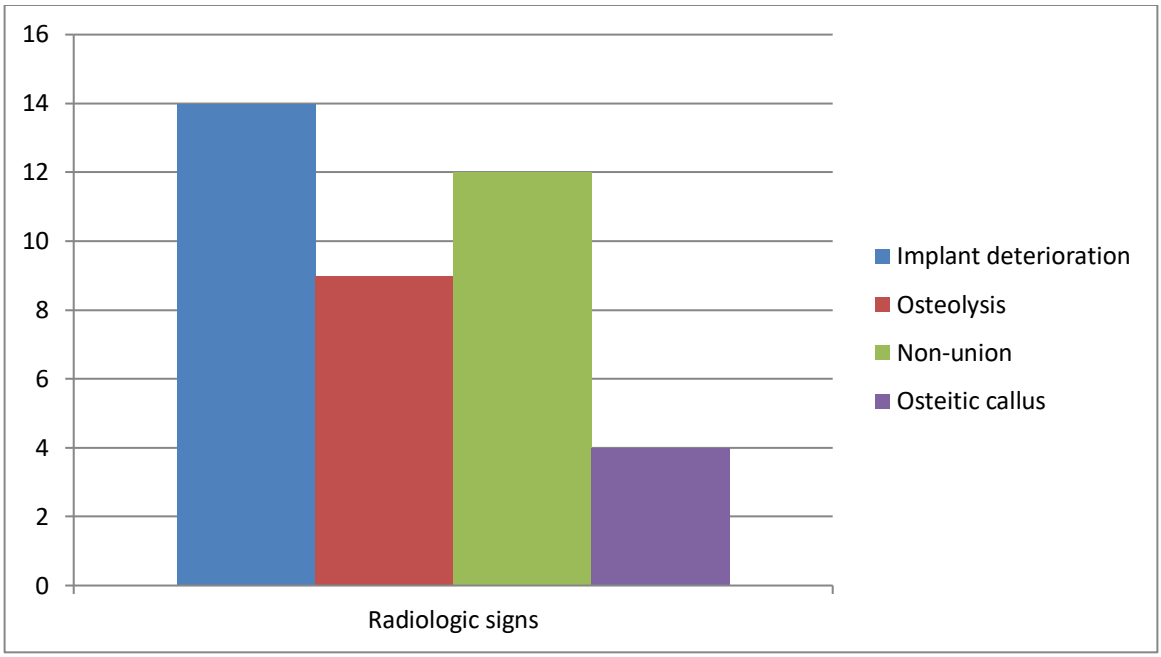

Fig. 8. Radiologic signs

6.2.7. Pathology of wound healing

13 patients (19.11%) had experienced wound healing difficulties in their past. Out of them, 7 patients (10.29%) suffered from wound dehiscence and 6 patients (8.82%) had suture granuloma development.

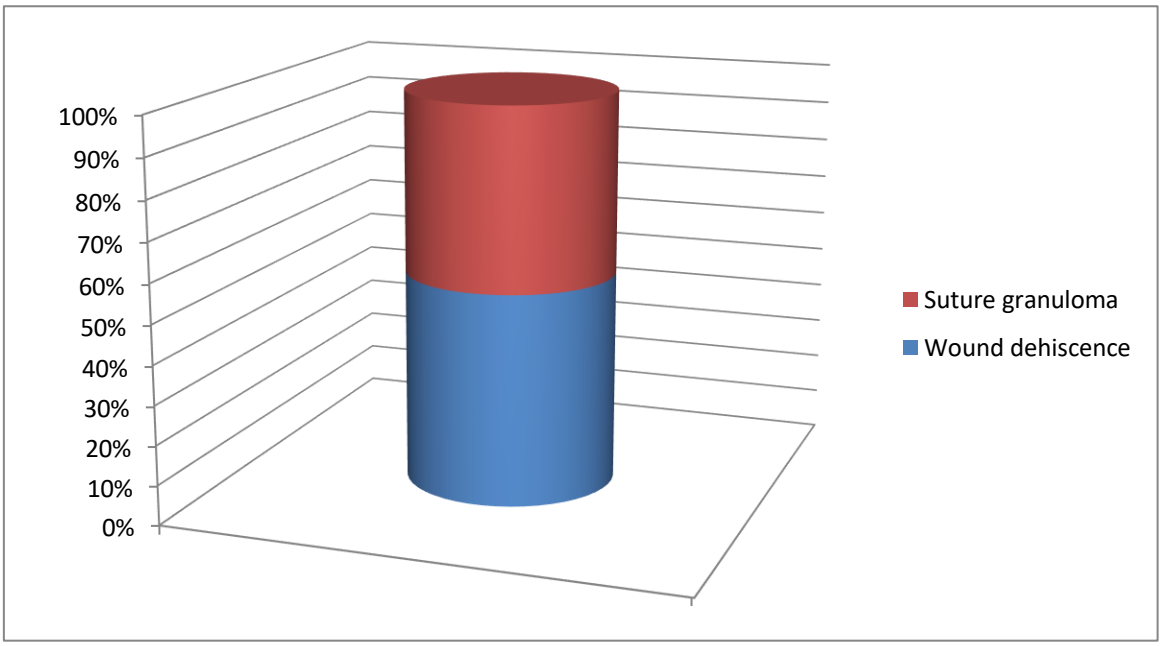

Fig. 9. Wound healing pathology

6.2.8 Local infection

Local infection at the site of the implant was detected in 11 patients. The diagnosis was made using culture testing from local secretions and through microscopic analysis of tissue samples. Staphiloccocus aureus was the most prevalent agent detected during testing (5 patients i.e. 45.45%), followed by Staphiloccocus epidermidis (3 patients, 27.27%), Pseudomonas aeruginosa (2 patients, 18.18%) and 1 case of Klebsiella pneumoniae infection (9.09%).

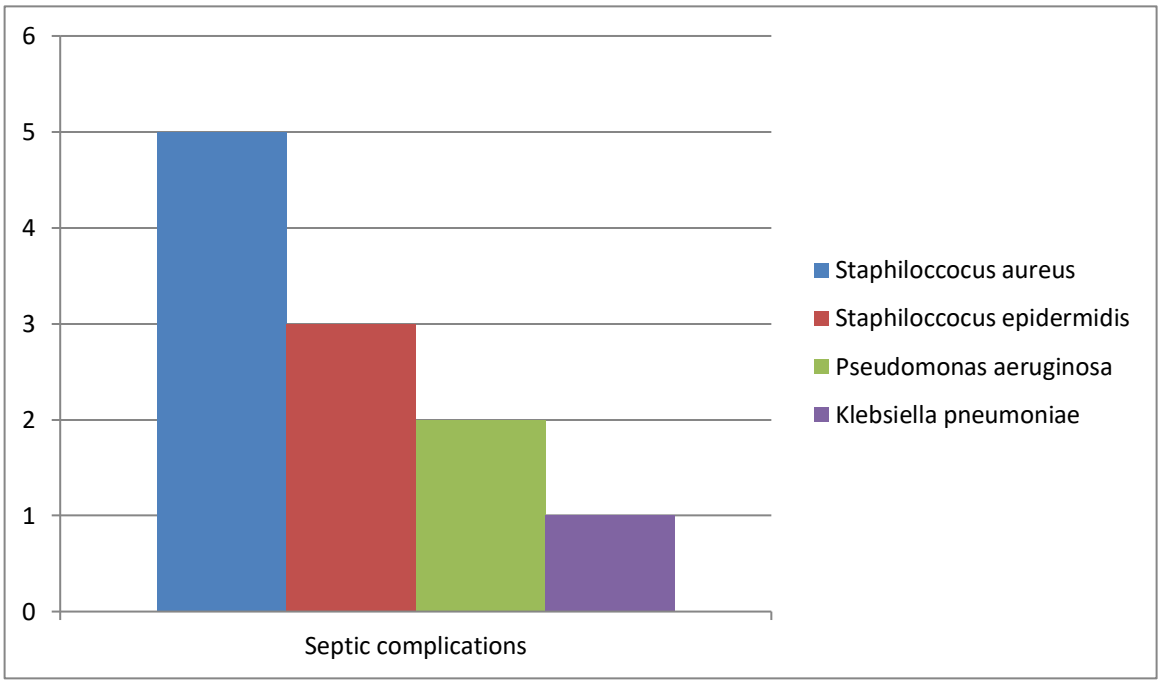

Fig.9. Local infection by agent

6.2.9. Peri-implant tissue intraoperative macroscopical analysis

Out of the 68 patients operated for implant removal, peri-implant tissue with fibrotic evolution was found in 46 of them (67.64%). 28 patients had metallosis surrounding the implant (41.17%), and in 6 patients (8.82%) suture granulomas have been discovered at the naked-eye analysis, intraoperatively. All the granulomas were caused by nonabsorbable threads used for suturing fasciae.

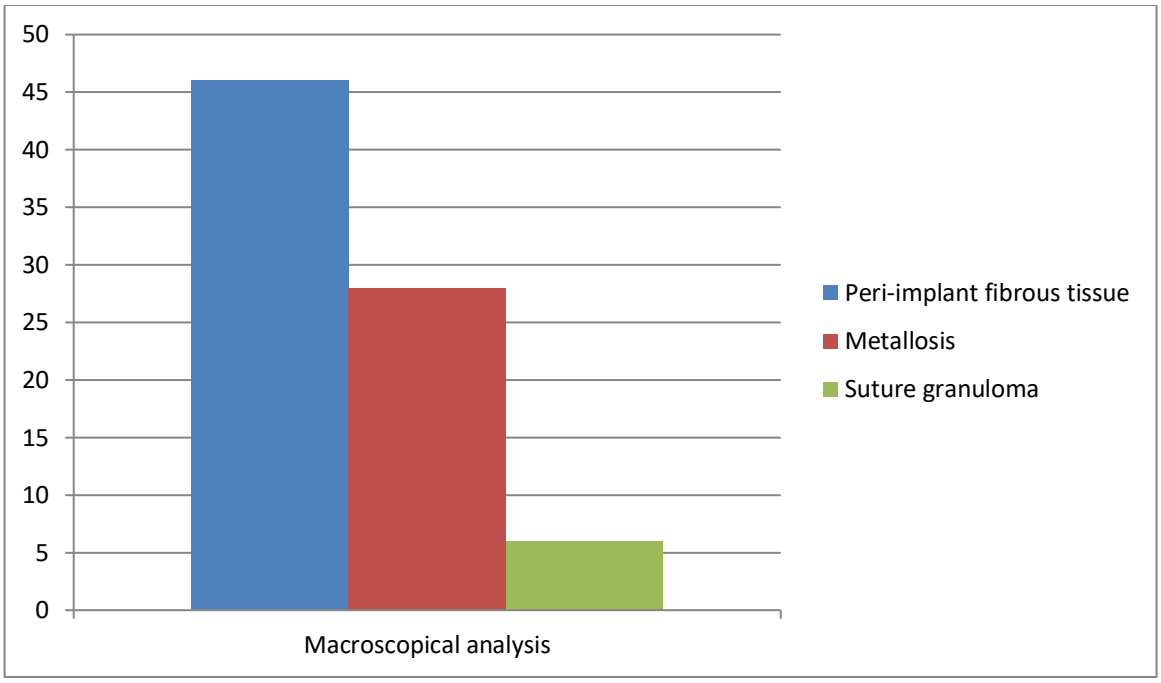

Fig. 10. Macroscopic analysis of tissues

6.2.10 Histopathological analysis of tissue samples by inflammation degree and cellularity

Types of tissue reactions to implant:

1. Acute prolongued inflammation / infection;
2. Chronic inflammation;
3. Foreign body reaction (macrophages and giant cell presence);
4. Fibrous tissue;

Acute prolongued inflammation is microscopically proven by specific cellularity (neutrophils, basophils, eosinophils, monocytes and macrophages) and was detected in 14 patients (20.58%).

Chronic inflammation was histologically described by the existence of lymphocytes, macrophages and plasma cells and it was found in samples from 21 patients (30.88%).

Foreign body giant cells were found in one third of the samples that were examined (24 patients, which represent 35.29%). 4 cases represented operated calf fractures (17%), 4 patients had distal humerus fractures, another 4 subjects had total knee arthroplasties done in the past, 2 patients had tibial plateau fractures (8%), 2 subjects experienced distal tibial fractures and the last 8 patients were operated for ankle fractures.

Peri-implant fibrous tissue was involved in 46 out of 68 patients.

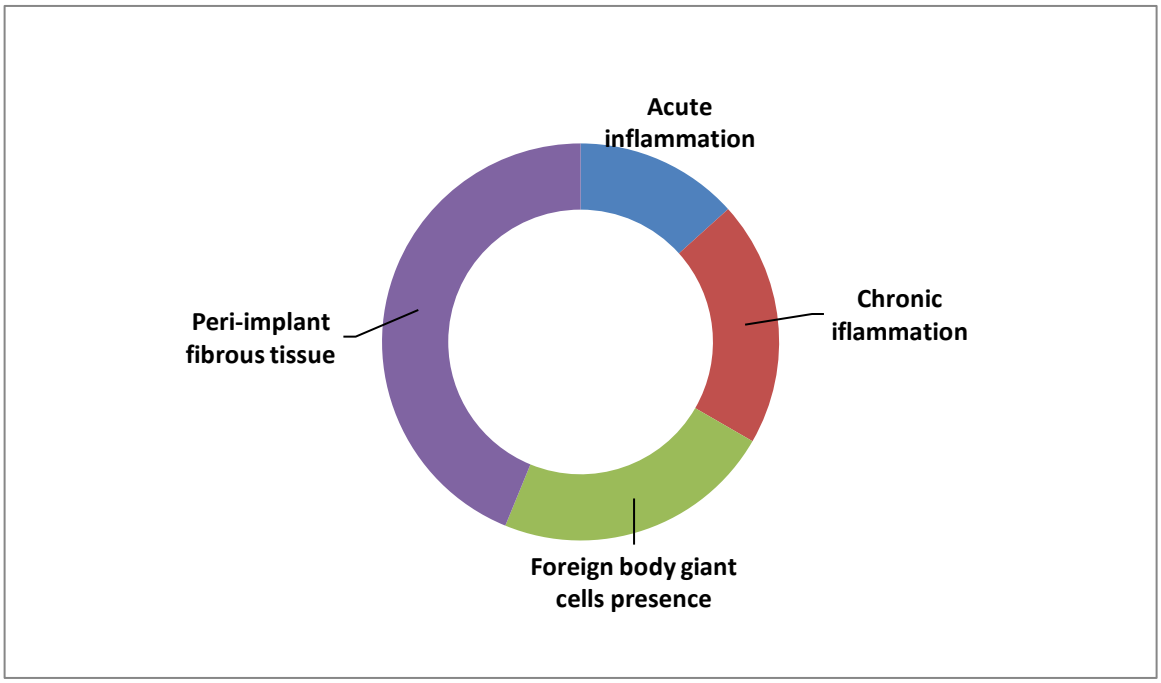

Fig. 11. Peri-implant tissue reaction types

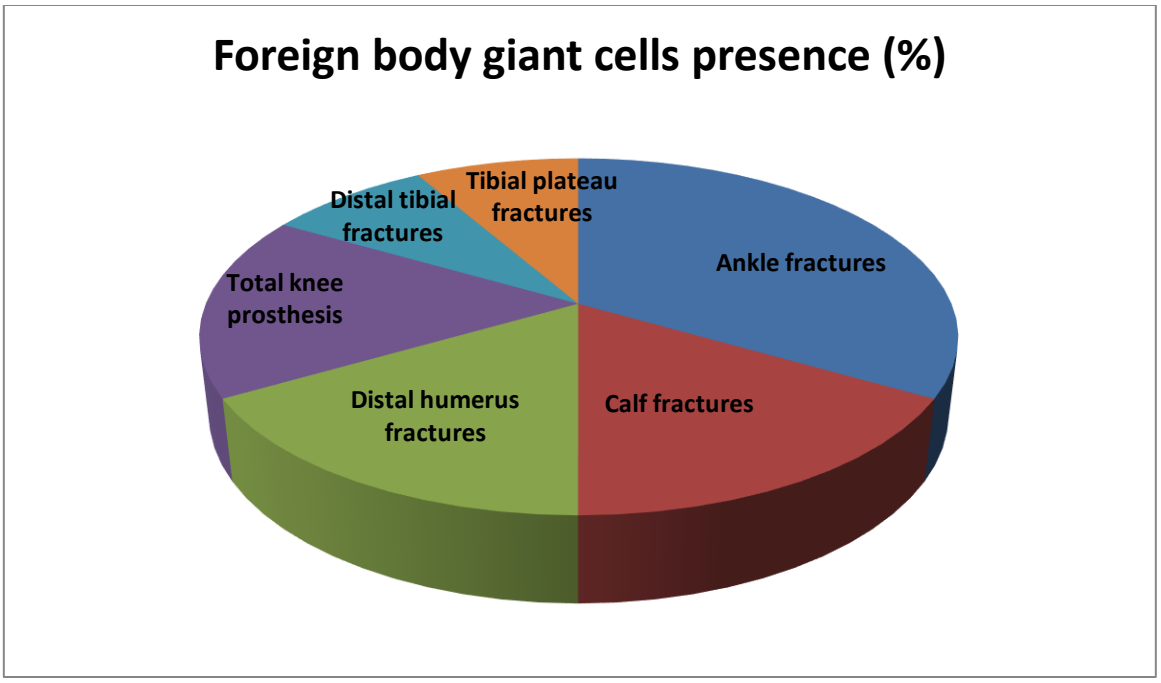

Fig. 12. Foreign body giant cells detection by implant position

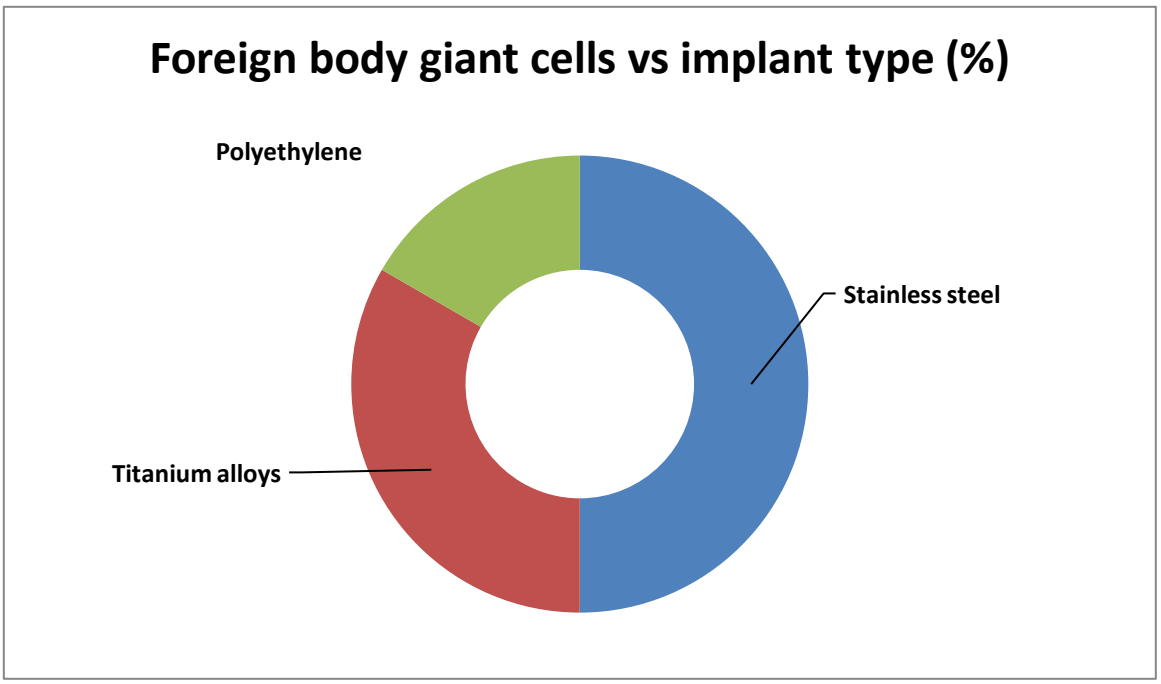

Fig. 13. Foreign body giant cells presence by implant type

6.3 Implant related factors

6.3.1. Type of implants

Among all cases studied, 5 patients had knee prostheses removal, 8 patients had hip prostheses removal, in 21 cases intramedullary nails were extracted and 34 subjects had paracortical plates taken out.

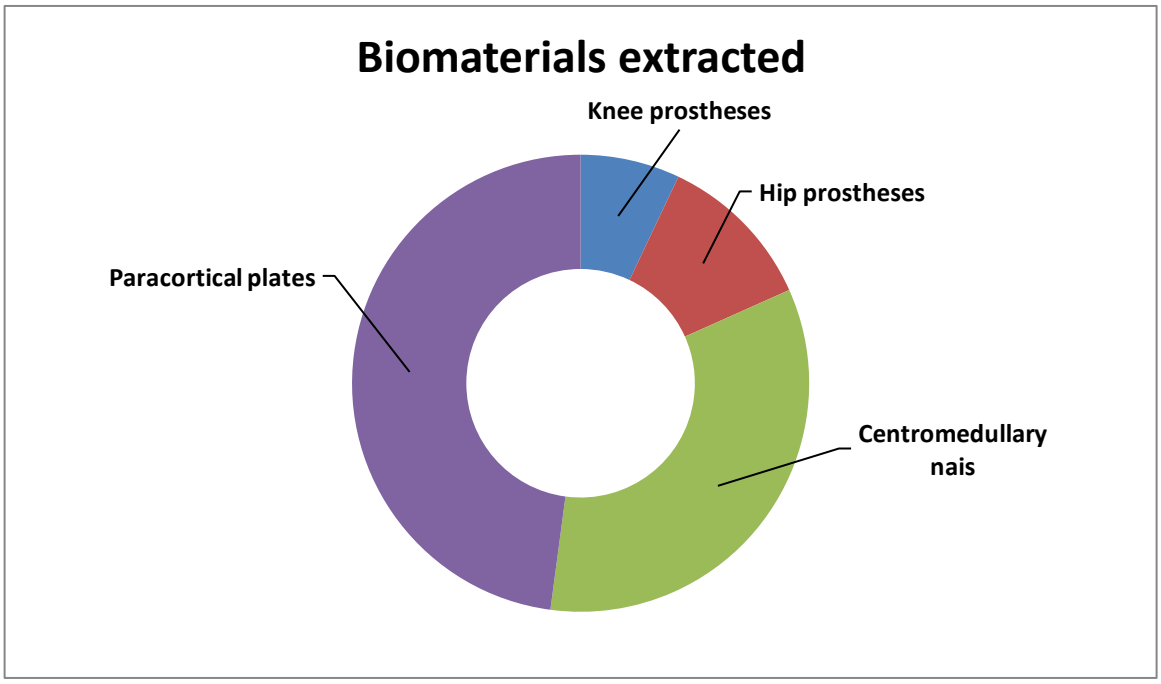

Fig. 14. Types of biomaterials extracted

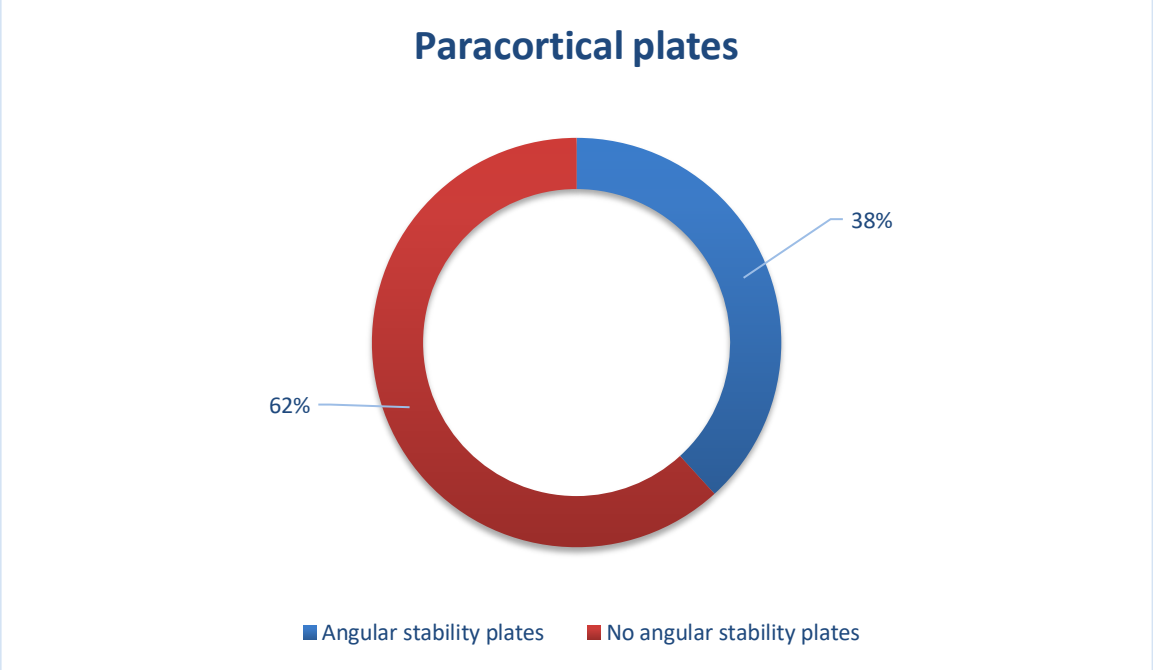

Fig. 15. Types of paracortical plates extracted

As stated in the above graph, the majority of plates which were extracted had no angular stability.

6.3.2 Structural components of the implants

When classifying implants by the type of alloy that was used, we identified 3 classes of biomaterials: ones containing biological stainless steel, others containing biological titanium and others having more than one biomaterial, like in the case of articular prostheses (CoCr – polyethylene, CoCr – polyethylene cross-link, ceramic). In our cohort of patients, 13 had associations of different materials, 24 had titanium alloys and 31 implants were constructed using mainly stainless steel.

Even though in our data, the prevalence of stainless steel implants is the highest one, giving the relatively small number of patients taken into account, there is no statistical proof that this trend exists in reality. We cannot stipulate, thus, that stainless steel implants are predisposed to local complications more often than others.

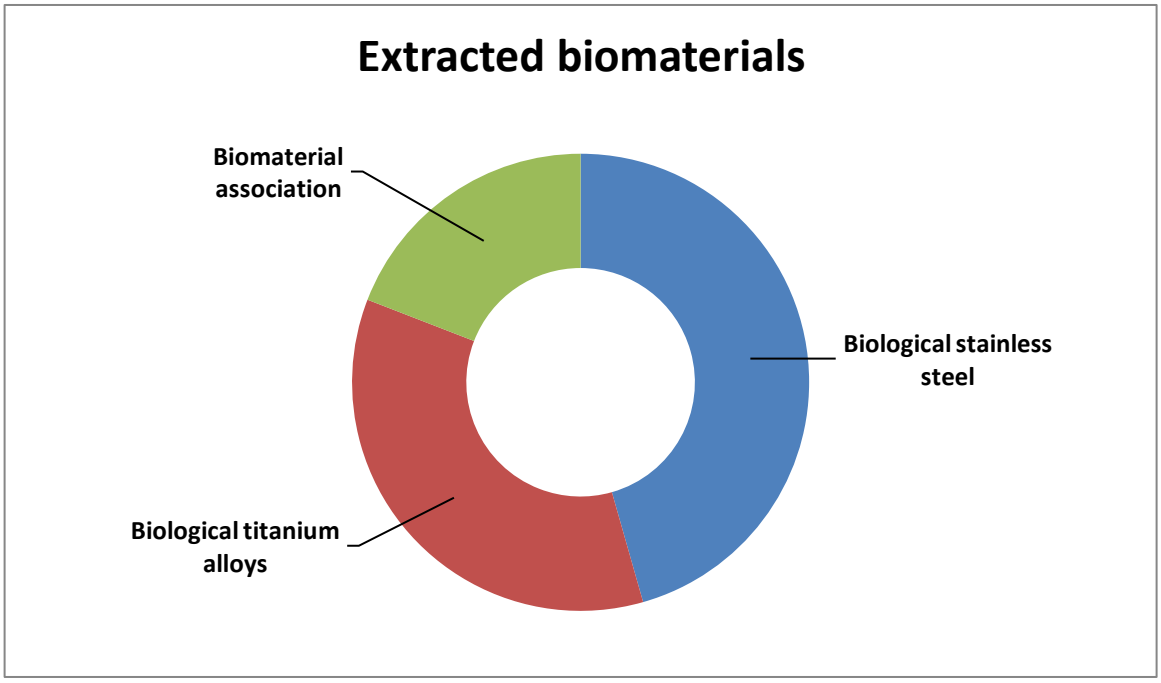

Fig.16. Implants by biomaterials used in their manufacturing

6.3.3. Type of implant coating

In this case we will consider only articular prostheses. Out of 13 patients who underwent arthroplasties, 8 implants had hydroxyapatite and 5 were coated with porous titanium. Even though the scientific literature stipulate that these coatings increase the biocompatibility at the bone-implant interface, we decided to test if there is an increase in local complications when using each type of implant coating. We should bear in mind that the number of patients with extracted prostheses is low compared with other types of implants. In our analysis there was not sufficient proof to clearly say if 1 type of coating or another had any influence over the complication rate. A higher number of patients should be used to make such predictions.

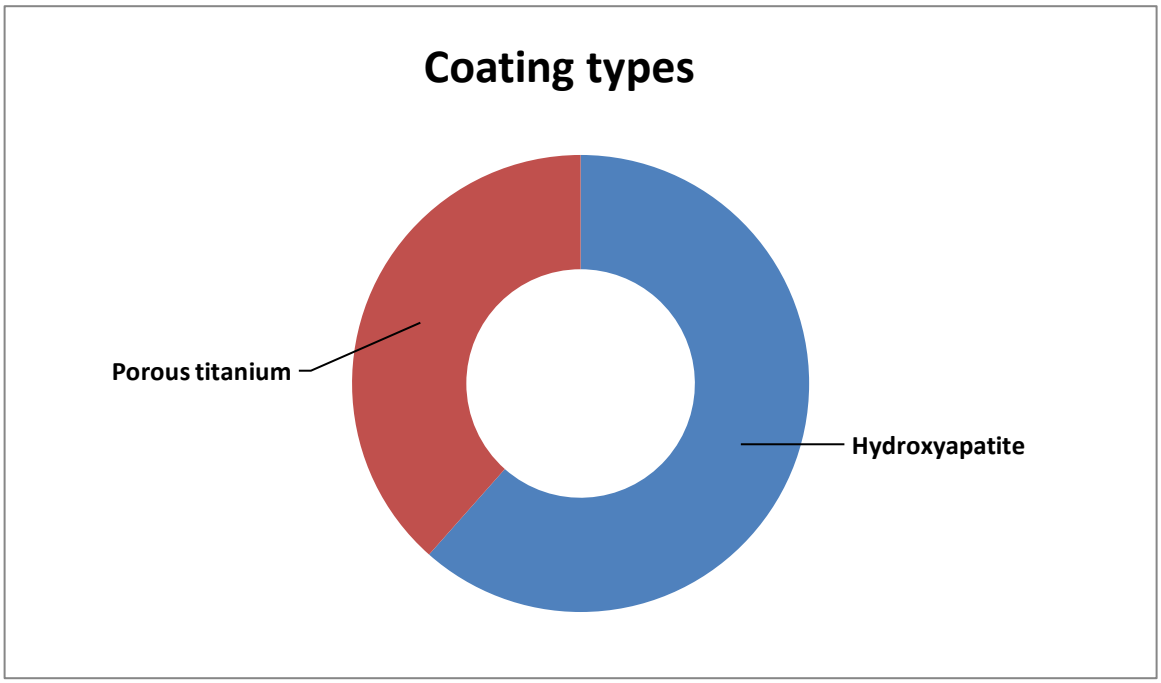

Fig. 17. Type of biomaterial coating

6.3.4. Period of time between implant fixation and implant removal surgery

We had split all 68 cases in 4 groups pertaining to the amount of time spent between implant fixation and implant removal surgery, in the following fashion: less than 3 months, 3 to 6 months, 6 to 12 months and more than 12 months since implant fixation surgery. It is worth mentioning that in our clinic we tend to wait for at least 12 months after the initial internal fixation, before we plan the implant's extraction.

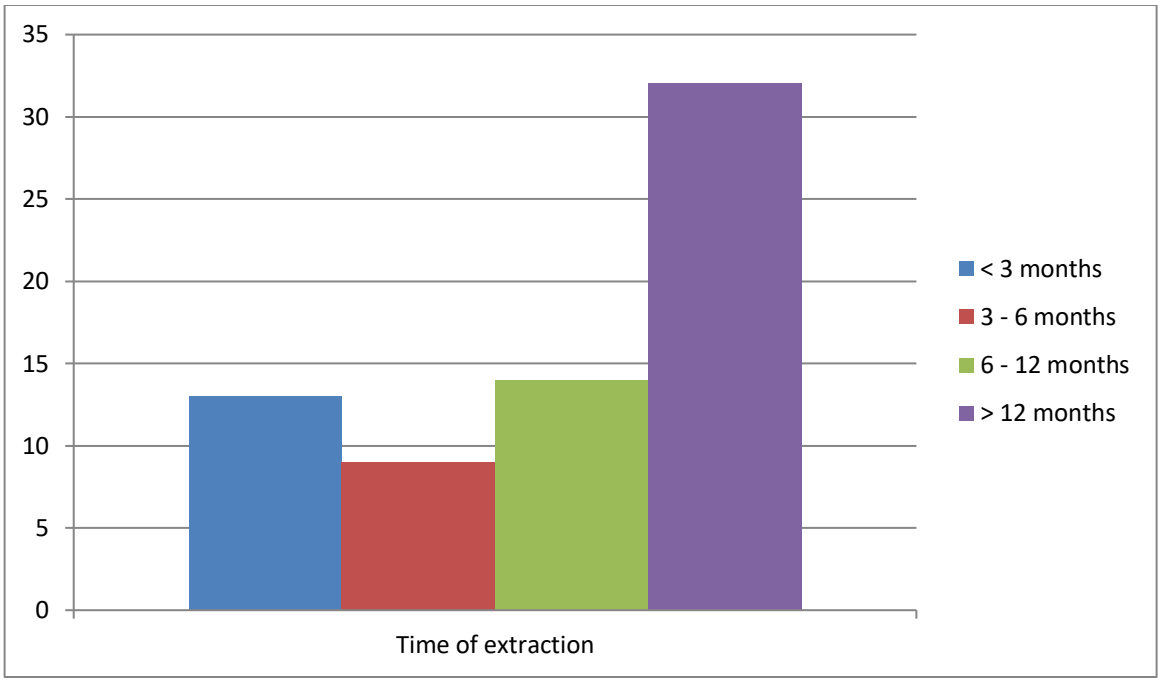

Fig. 18. Time periods between implant fixation and extraction

In the hereby study we tried through data processing to make correlations between patient related and implant related factors. The aim was to indentify predisposing factors that generate local inflammation and tissue altering. These changes can and will determine local complications and the implants' removal.

The correlations we made during our research, in accordance with scientific data are the following:

1. „Peri-implant tissue metalic impregantion, also called „metallosis" tends to happen more often in the case of stainless steel implants compared to the titanium ones." This correlation proved to be statistically significant (**p=0.045**). Moreover, foreign body giants cellularity was more frequent dicovered in tissues surrounding stainless steel implants than in those adjoining titanium implants (**p=0.032**). The difference in statistical significance is caused by the fact that the evaluation of metallosis is a macroscopic identification by the surgeon, whereas histopathological analysis is more precise and easier to reproduce.

2. „Local acute inflammation was more intense near stainless steel implants compared to titanium implants". The correlation is in fact real **(p=0.043).** Pathology assesment showed inflammatory cellularity (neutrophils, basophils, eosinophils, monocytes) pertaining to acute inflammation. However, chronic inflammation was proven not to correlate with the type of implant used **(p>0.05).** This correlation supports the findings of James Anderson [129] who demonstrated the importance of biomaterial-tissue interface in promoting iflammation. Following fixation, after contact between blood and the outer surface of the implant, acute and chronic inflammation ensues. The severity of these reactions is dependent on the extent of surgical maneuvers during implantation, on the tissue type and on the characteristics of the biomaterial. The acute phase of inflammation is described by neutrophil cells activity, mastocytes' histamine release and fibrinogen adsorbtion on the surface of the biomaterial. As stated before, these changes are more prominent in the presence of stainless steel implants, and less severe around titanium implants. Chronic inflammation is not so consistent histologically (albeit there's an increase in monocytes and lymphocytes levels) and it is not dependent on the type of implant. If chronic inflammation exceeds 3 weeks, there is an increased risk of local complications like infection and giant cells cellularity.

3. „Naked eye metallosis was less frequent in angular stability plates compared with classic paracortical plates". This assumption was statistically significant (**p=0.039**). In this case we cand freely say that classic paracortical plates pose a risk of metalosis. A good explanation is that plates provided with angular stability are more often made out of titanium, not stainless steel. Additionally, classic plates use cortical screws that can easily become loose in ostheoporotic bones. Meantime angular stability plates provide screws with great stability irrespective of bone density.

4. „Local infections are more frequent in patients with stainless steel implants compared to titanium implants". This hypothesis proved wrong during our statistical analysis (**p>0.05**). As stated above, only acute inflammation is influenced by the type of biomaterial involved, whereas chronic inflammation does not correlate with such aspects. As is generally perceived, the infectious process is more or less a result of

chronic inflammation and an exacerbation of the immune system. This explaines our finding.

5. „Local skin reactions at the site of the surgical intervention correlate more often with a history of allergies and dermatitis". We identified 18 patients with a history of allergic reactions or dermatitis. Out of them, 3 had contact dermatitis to metallic products (buckles, jewellery), 5 patients had allergic asthma, 3 patients experienced allergic reactions to certain foods and 7 subjects presented with allergies to certain drugs. This assumption did not prove itself during our analysis **(p>0,05).** A setback in this case is the small number of patients with contact dermatitis, available for the study. We consider that more research on this matter is necessary.

6. „The intensity of the surgery site inflammation decreases as time passes after the fixation procedure." This hypothesis was statistically significant **(p=0.039)** during our data compiling. We can be confident that in our patient cohort, the local inflammation diminishes with time spent since the fixation procedure. This statement is true for both titanium and stainless steel implants.

7. „The extent of surgical intervention generates more inflammation and increases the risk of local infection". In this study we tried testing if the operative technique employed during surgery affects the intensity and duration of local inflammation. The value of p for this correlation was **p=0.046** which proves our point. Although inflammation quantification is a difficult task, there were instances when abundant inflammatory cellularity was described in implant removal surgeries using the open technique (in dia-meta-epyphiseal fractures). Having in mind that in this type of fractures we tend to use more often angular stability plates (low inflammation index), it is reasonable to say that the operative technique still plays a part in generating inflammation. More research needs to be done on this subject, employing more patients and perhaps comparing different surgical techniques on the same body part.

7. Discussions

The tissular reaction to implants is a central point of interest in today's orthopedics practice, because most of the surgical interventions performed in this field employ the usage of implantable biomaterials. Although testing nowadays is rigorous and the implants' quality is most of the time adequate, Anderson et al. [129] have shown that once implanted, biomaterials produce inflammation through local chemical pathways. Also, the same research team have proven that the degree of inflammation produced locally is dependent on the biomaterial employed. As it has been stated before, implants made out of stainless steel are prone to producing local inflammation, macsoscopical metalic impregnation, which can be demonstrated on microscopical analysis.

For the last 30 years the potential problem of choosing the right type of metal for the implants, the corrosion properties of metals and the giving off of compounds in the blood stream, has been actively debated. Thomas et. al. [130] succeeded to create a correlation between peri-implant inflammatory scores and metal corosion scores irrespective of patient's symptoms. This testing was conducted through thorough microscopical analyses. Moreover, inflammatory scores have also been linked to the time spent by implants in situ, tissular reactions decreasing with the time spent since the fixation surgery. This suggests that the corosion compounds eliminated by stainless steel implants are well tolerated by the surrounding tissues. Those compounds produced locally must certainly decrease over time.

Even though our study didn't aim to extract and calculate the corosion scores of biomaterials, it has nevertheless proven that stainless steel implants determine far higher levels of metallosis than titanium implants. The explanation is probably, that stainless steel produces over time corosion compounds that stain the tissues (metallosis) and attract inflammatory cells nearby. The same results were also presented by Thomas et. al. [130] in their paper. The correlation was also proven in the case of giant multinucleated foreign body cells. This type of cellularity was common in tissue adjoining stainless steel implants.

Another worth noticing study was done by French et. al. [131] who came up with the same conclusions as Thomas. Moreover, he demonstrated that the intensity of inflammation decreases over time.

In his 2019 study, Haddad et. al. [128] elaborated a review of the prevalence of metalic allergies in the general population. He showed that people with or without any history of dermatitis still produce allergic reactions when patch-tested to metals. Nickel was the most frequent metal to trigger allergic reactions in people. Those with dermatitis caused by other agents had a 5 fold increase in allergic reaction probability when tested to nickel. Paladium, copper and cobalt are other „culprits" in provoking allergies. In our study we could not test his findings because there were only 2 patients with dermatitis history. However, we consider that this hypothesis must be put to the test in bigger studies, because orthopedic materials can trigger local and general allergic reactions with various consequences.

We would like to state the importance of skin inspection in patients who undergo orthopedic interventions, because this is usually where the intolerance to biomaterials is first time revealed. Complications like cellulitis and local inflammation can become chronic and they can also have a general impact in one's health. Fungi can also cause local infections at the site of the implant, as shown in a previous case report. In all cases, alongside antibiotic/antifungi treatment, implant removal is mandatory. Thus, the cause of infection is eliminated and the treatment will be more efficient.

8. **Conclusions**

1. Out of 68 patients included in the study, who underwent implant removal surgery, 28 had presented metallosis during macroscopical assessment. This implied that no matter what material is used, there is no substance or metal that is completely inert to the surrounding tissue influence. Once implanted, biomaterials will make contact with bodily fluids and will cause inflammation over time.
2. Metalic staining during naked eye observation in the surrounding tissues (metallosis), happend more often in the case of stainless steel implants, in opposition to the titanium ones;
3. Foreign body giant multinucleated cells appear more frequently in tissues adjoining stainless steel implants and less in the case of titanium implants;

4. During histopathologic assessment of tissue samples exhibiting acute inflammation, the most prevalent type of cells were: neutrophils, bazophils, eosinophils, monocytes. There was significantly more inflammation in case of stainless steel implants than titanium ones.
5. Macroscopic metalic staining (metallosis) was less severe when angular stability paracortical plates were being used instead of classic plates.
6. Local infectious complications had the same rate of ocurrence in tissues adjoining both titanium and stainless steel implants.
7. The extent of local inflammatory response, quantified during microscopical analysis, decreases with time passed since the moment of surgical fixation. This result is valid for both titanium and stainless steel implants.

9. Paper's originality

We consider that the study's originality consists in the histopathologic analysis of peri-implant tissues in both symptomatic and symptom-free patients. In addition to that, beside the microscopic overview and cellurality quantification, there was also a macroscopic assesment done during surgery. During scientific literature information sessions we did not discover any recent studies that apply the protocol stated above on non-symptomatic patients. We strongly believe that additional research on this subject should be performed.

10. Innovative contributions brought out by this study

The hereby study brings out to the orthopedics scientific community new approaches like: peri-implant tissue analysis, the evaluation of biomaterial generated inflammation. Unfortunately, after many orthopedic surgeries, peri-implant complications are being overlooked in favor of functional outcome. This study helps the community to realize that no biomaterial, no matter how advanced, can achieve complete biological inertion once implanted. Consequently, in order to avoid unwanted complications for the patient, we should always bear in mind the constant interaction between implant and local tissues.

11. Study limitations

The most important setback during the elaboration of this paper was the relatively small number of patients taken into account. The original estimates of 100 patients has been downshifted to 68 because of the Sars Cov 2 Pandemic that prohibited ellective surgery being done in our clinic.

Moreover, there were only a few patients with allergies in their history, which made it difficult to make correlations with the implanted biomaterial.

12. Future research approaches

It is desirable to introduce patch-testing to all patients with history of allergies, before surgical intervention, in order to evaluate one's sensitivity to metals. Concurrently, high value correlations can be made only when sufficient numbers of patients are included in the studies. This in turn increases statistical significance.

Another future course for this research is the incorporation of patients with periprothetic infections. This will further improve the study of metal associations used in prostheses construction and its interaction with the human body.