

## Modern possibilities with early laboratory diagnosis of periprosthetic osteolysis predating aseptic loosening in total hip arthroplasty (literature review)

S.V. Bragina

Northern State Medical University, Arkhangelsk, Russia

Implant survival is a very important outcome measure of surgical treatment of patients with severe degenerative joint disease in the hip. **The aim** of this review is to summarize the present knowledge on the possibilities for earlier laboratory diagnosis of osteolysis and prognostic approaches to prevent aseptic loosening of prosthetic implants. **Results** Periprosthetic osteolysis is often seen as an early sign of an adverse event associated with the development of unstable total hip arthroplasty (THA). A lot of data support the concept of osteolysis as a condition caused by biomechanical stresses, surgery specific factors, preoperative decrease and postoperative loss of bone mineral density, vascular impairment and chronic inflammation. Hemostasiological, biochemical and immunological parameters of patients were explored before and after THA. Surgical intervention was treated as the cause of secondary immunodeficiency, and results of the recovery period evaluated with regard to the extent to which immunodeficiency appeared to be compensated. Dynamics in stress related bone remodeling around the implant was found to be a marker for early detection of osteolysis and prediction of aseptic loosening of THA, as well as control over the "target" of drug exposure. **Conclusion** Literature review suggests that there is a common understanding of the pathogenesis of osteolysis and the development of aseptic loosening of THA, and there is scanty data on the laboratory markers for early diagnosis and prediction of the complication that would require further study.

**Keywords:** total hip arthroplasty, osteolysis, endoprosthesis loosening, prediction

### INTRODUCTION

Since the time Sir John Charnley designed a hip prosthesis total hip arthroplasty (THA) has evolved into one of the most successful orthopedic procedures performed today. There has been an increase in the number of primary and revision THAs performed worldwide [1, 2]. Aseptic loosening is a major complication of joint replacement and it is important to identify factors potentially associated with the adverse event [3–

8]. Despite the large number of publications on complications following arthroplasty and extensive discussions in orthopaedic forums, controversies exist regarding potential prognosis and prophylaxis of adverse events of THA [9–15].

**The aim** of this review is to summarize the present knowledge on the possibilities for earlier laboratory diagnosis of osteolysis and prognosis to prevent aseptic loosening of prosthetic implants.

### RESULTS

While the global medial research efforts focus on different aspects of osteoarthritis orthopaedic and trauma surgeons continue to perform radical procedures replacing the native joint with endoprosthesis for severe conditions. Total joint arthroplasties have revolutionized the care of patients with end-stage joint disease, leading to pain relief, functional recovery, and substantial improvement in quality of life. The longer patients use endoprosthesis the higher is the risk of implant loosening [16–20]. J.B. Meding et al. reviewed 8331 primary THAs to determine the greatest risk of failure across time. The average time to failure was 9.2 years, and 75 % of failures occurred by 13 years. The most common failure mechanisms were due to the cup (5.0 %), cup and stem (1.7 %) and the stem (0.4 %). Based on the most common failure mechanisms, the

authors recommended to evaluate patients at 6 months, 1 year, 3 years, 7 years, 10 years, 12 years, 18 years, and 25 years postoperatively [21].

Aseptic loosening occurs in dynamics at a long term with the implant being stable and osteointegrated over a protracted period that can be followed by bone resorption at the periprosthetic site with the bone being replaced by spongy connective tissue with infiltrated macrophages and implant-derived wear particles. Aseptic loosening secondary to periprosthetic osteolysis has been accepted as one of the leading causes of revision procedures in 2/3 patients with previous joint arthroplasty [22–24]. The impact of periprosthetic osteolysis on THA ranges between 1 % and 40 % of all THA revisions [25–27]. A major concern in periprosthetic osteolysis is that patients may have no clinical manifestations, no suggestion of

any sign of infection, effectively remaining completely asymptomatic [28–31]. Although Sir John Charnley suggested that aseptic loosening could be caused by subclinical infection, recently it has been recognized that aseptic joint replacement loosening cannot be driven by bacterial infection, and underlying mechanisms are being searched [32]. Aseptic loosening may occur due to the biological response of the bone to fluctuating intra-articular fluid pressure, stress shielding and micromotion at the bone-implant interfaces [33]. The process referred to as particle disease often leads to joint loosening and implant failure [23, 28, 30]. Wear of endoprosthetic components gradually sets in due to mechanical surface interactions between bearing surfaces of the implants and the bone with a lot of implant-derived wear particles migrating into the pseudosynovial fluid and the surrounding tissues. The characterization of wear particles (size, shape, chemical composition) ranges depending on the origin and individual response of the body.

Those are mostly ultra-high molecular weight polyethylene (UHMWPE) wear particles generated from the bearing implant surfaces with the metal prosthetic femoral head and a polyethylene liner being involved in the pathways with a mean linear wear rate of 0.1 mm/year forming numerous UHMWPE particles [29]. Metal-to-metal implants have less wear than metal-to-polyethylene implants but still with release of numerous nano-sized metal particles [34]. Additional sources of wear include increased shattering and greater fragmentation of polymethylmethacrylate particles, metallic or ceramic particles released from bearing surfaces or modified implant surfaces [28, 30, 35]. The particles released into pseudosynovial fluid are accumulated in the surrounding tissues under the influence of hydrodynamic forces being generated in the fluid with every step and the environment appears to be densely packed with biomaterials of different wear particles. UHMWPE particles tended to exhibit many different morphologies over a number of size ranges. Particles of UHMWPE are assumed to be spheroids with the diameter of 0.1 to 1.0  $\mu\text{m}$  (mean diameter ranging from 0.5 to 0.7  $\mu\text{m}$ ) [36, 37]. It has been recognized that wear debris stimulates an innate host immune response leading to chronic low-grade inflammation and finally, to osteolysis [28–31, 34]. The foreign body response with macrophages and foreign body giant cells is identified leading eventually to predominance of osteoclasts at bone-soft tissue interface. Biomechanical and tribological aspects are considered to be crucial in pathogenesis of implant failure. Those include functional overloading, surgery specific failures, preoperative decrease and postoperative loss of bone mineral

density, vascular impairment and slow blood flow, hypercoagulation, injury to vascular wall secondary to vasoconstriction deteriorating in the operated limb postsurgery, synovitis, generated wear debris in the tissues having a key role in the progression of the disease with numerous proinflammatory cytokine secretion [28, 29]. Surgical aggressive approach in arthroplasty includes volume of intervention, the traumatic profile, blood loss and can cause secondary immunodeficiency and/or aggravate the patient's condition [38].

Biological interactions are explored with an implant's integration in the human body in addition to the aspects of mechanical wear of endoprosthetic components, and biochemical reactions of the symbiosis can be unpredictable. Endoprosthesis is placed into aggressive and dynamic physiological environment and introduces mechanical loading causing non-specific reactions and launching specific immune mechanisms [34]. Immunopathological features and changes in immune function during perioperative period are responsible for postoperative rehabilitation and the outcome. E.V.Gladkova et al., I.V.Chebotar focused on hemostasiological, biochemical and immunological tests examining peripheral blood films of patients preoperatively, at 4 to 5 months postsurgery, analyzing three leukocyte subpopulations (lymphocytes, monocytes, granulocytes) and immunophenotyping lymphocytes. Preoperative and postoperative blood test results indicated to expressed immune disorders in patients with osteoarthritis of major joints of lower limbs. Postoperative changes in the blood tests exhibited humoral and cell-mediated immune deficiencies that were shown to interfere with adequate protective response to aggressive operative treatment with arthroplasty [39, 40]. E.V.Koryakina et al. explored preoperative immune status of patients and detected activation of proinflammatory cytokine (FNO $\alpha$ , IL-1 $\beta$ , IL-6) associated with changes in concentration of anti-inflammatory cytokines (IL-4, IL-10). The authors suggested that preoperative lack of functional activity of T-helpers led to immune deficiency in patients with osteoarthritis [41]. Low phagocytic activity of segmented neutrophils, high levels of T lymphocytes, B lymphocytes and immunoglobulins were reported in revision THA cases [42–44].

L.A. Dmitrieva reported increased serum concentration of IgA and high level of proinflammatory cytokines produced in the peripheral blood cells of patients with severe dysplastic coxarthrosis that necessitated grouping of dysplastic coxarthrosis cases depending on severity and type of immunopathological reactions (conventionally compensated and

subcompensated immunodeficiency). There was correlation observed between outcomes of surgical treatment and rehabilitation, and the extent to which immunodeficiency compensated.

The differences in the immune status and the pituitary-thyroidal link of the endocrine system noted in patients with compensated immunodeficiency facilitated favorable restorative period and minimal risk of postoperative adverse events. Alternately, patients with subcompensated immunodeficiency failed to hold a capacity to ramp up a protective mechanisms to surgical intervention and were identified as high-risk patients at different terms [45]. E.A.Volokitina et al. explored an immune response to surgical intervention in patients with hypoplastic coxarthrosis following THA and reported a slight increase in natural killer T cells (CD3+/CD16+/CD56+) during the first postoperative month. The authors detected the absence of profound disorders in the functional immune system with the favorable scenario with major humoral and cell-mediated immune parameters returning to baseline values at 18 to 21 days following THA. Moderate decrease in T cell count, imbalance of lymphocyte subpopulations, dysimmunoglobulinemia were noted with increase in weight-bearing on the operated limb at 3-to-6-month follow-up. Major cell-mediated immune parameters normalized and absolute numbers of T-helper cells and B-lymphocytes decreased at 7-to-12-month follow-up with no history of early and delayed postoperative complications. Normal levels of serum immunoglobulin of primary classes and circulating immune complexes were observed during the first year following THA [18].

Postoperative clinical manifestations of pain, limping, disturbed function of the operated joint

without evident radiological signs of radiological implant loosening are indications for exploring biochemical parameters for diagnostic purposes. Biochemical criteria were offered for prognosis and early diagnosis of aseptic loosening prior to clinical manifestations [46]. E.A.Persova found that changes in the blood serum biochemical markers identified after THA anticipated alterations in bone mineral density with stress induced remodeling being detected at 1.5 to 3 months [47]. S.Yu.Istomin reported on comparative analysis of clinical and radiological findings and lipid peroxidation parameters establishing correlation between instability of endoprosthetic components and increased concentration of isopropanol soluble products of lipid peroxidation, decreased ascorbat induced lipid peroxidation, and found the metalloprotein concentration being responsible for control of postoperative period [48]. Specific bone metabolism markers have been widely used for early diagnosis and identification of risk factors leading to aseptic stem loosening in THA. A.E. Kearns et al. suggest that polypeptide growth factors and cytokines are involved in osteogenesis and bone resorption and receptor activator of nuclear factor kappa-B ligand (RANKL), a member of the tumor necrosis factor cytokine family, promotes terminal differentiation of osteoclast precursor cells and stimulates bone-resorbing activity of mature osteoclasts [49]. Such cytokines and molecular factors as interleukins (IL) IL-1 $\beta$ , IL-6, IL-8, IL-11, IL-17, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), macrophage inflammatory protein-1 $\alpha$ , prostaglandin E and others can induce the synthesis of RANKL with bone marrow stromal cells including osteoblasts, T lymphocytes and B cells [50-56].

## DISCUSSION

In this review we sought to summarize the present knowledge on the pathogenesis of periprosthetic osteolysis followed by the development of aseptic loosening of THA, possibilities for earlier laboratory diagnosis and prognosis of the adverse event. Being aware of the causes of aseptic loosening of THA as a chain of biomechanical reactions in the implant-host system, tribological implant characteristics, surgery specific failures specialists put forth their efforts in attempts to increase implant longevity. In addition, other factors can be involved in the pathogenesis of aseptic loosening in a particular case. There is a search of markers that would enable prediction of this threatening complication prior to THA or diagnosis of osteolysis as early as possible to prevent considerable bone loss. Hemostasiological, biochemical and

immunological parameters of patients are explored before and after THA. There is an interest in studying specific features of immune status among phenotypical groups of patients with dysplastic and hypoplastic coxarthrosis. A surgical intervention is treated as the cause of secondary immunodeficiency, and results of the recovery period evaluated with regard to the extent to which immunodeficiency appears to be compensated. Potentially critical differences exist between biological mechanisms of primary, age-associated, post-traumatic and metabolic phenotypes of osteoarthritis. Dynamics in stress related bone remodeling of periprosthetic bone tissue can be a marker for early detection of osteolysis and prediction of aseptic loosening of THA, as well as control over the "target" of drug exposure. A prospective clinical observation of the anticipated development of

the adverse event allows for timely detection of aseptic loosening. Further research on the sensitivity and specificity of the above parameters is required since, with the current knowledge of the pathogenesis of the

chronic inflammation, they can be observed in a variety of nosologies including osteoarthritis/osteoarthritis, systemic rheumatic diseases, metabolic syndromes, malignancies and other conditions.

## CONCLUSION

Literature review suggests that there is a common understanding of the pathogenetic reactions at the bone-implant interface, the effects of particular biomechanical, tribological factors on the development of periprosthetic osteolysis followed by aseptic

loosening of THA. Scanty data on the possibilities for early diagnosis and prediction of the complication require multidisciplinary research for the understanding of systemic approach to a range of conditions with identical markers involved in pathological reactions.

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#### Information about the author:

Svetlana V. Bragina, M.D., Ph.D, Assistant Professor  
Northern State Medical University, Arkhangelsk, Russia,  
Email: [svetabragina69@mail.ru](mailto:svetabragina69@mail.ru)