Title: **Report on HyperBaric Oxygen (HBO_2) in femoral head necrosis**.

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INTRODUCTION

Femoral Head Necrosis (FHN), also named AVascular-Necrosis (AVN) or OsteoNecrosis (ON) of the femoral head (FH) [AVNFH-ONFH], is a multifactorial disease that can result in a significant clinical morbidity and can affect patients of any age, including young and active patients.

Among the many possible late sequelae of a femoral head osteonecrosis this might result in femoral head collapse and the subsequent hip joint degenerative lesions (Shah KN) [32].
At the present time there is an increasingly refined radiographic evaluation that is allowing any orthopaedic surgeon to clearly identify this disease at an earlier stage than ever before (Aaron RK) [1].
The current operational choices and therapeutic standards, that are nowadays well-defined for management and care of a hip osteonecrosis do show results that differ from each other accordingly to the specific patient population and the disease stage considered.
Some emerging sophisticated technologies have led to the development of case-management strategies that may be able to positively alter the course of a femoral head osteonecrosis (Amanatullah DF) [3].
ONFH is essentially that final common pathway of a series of structural derangements, resulting in a sharp decrease in provisional blood flow to the femoral head, leading to the cellular death, fractures, and collapse of the articular surface (Herndon JH; Mwale F) [16, 25].
In the United States, and generally speaking in the western world, its prevalence stands at 39 y.o., as per mean age, and it is considered responsible for the 5÷18% of hip replacements performed.
From a nosographic point of view what is identified as an avascular hip osteonecrosis is the usual outcome of that unrelenting course gradually heading to a functional loss of the hip.
It is actually such a rare occurrence to have spontaneous regression of an AVN; most of the untreated (67% of asymptomatic patients and 85% of symptomatic hips) proceed in fact towards femoral head collapse (Musso ES) [26].
Although many authors have already suggested and advocated a treatment based on patient's age, symptoms, stage, and/or medical status, the orthopedic community has not yet adopted a univocal algorithm for the treatment.

ON PATHOPHYSIOLOGY:

The limit to a complete comprehension of ON risk factors and inherent pathophysiology is the lack of a bipedal mammalian model as well as the unavailability of longitudinal studies in humans.
Hallmarks of ON are specific and have a typical pattern of cellular death and a complex process of bone resorption and formation. ON first pathologic presentations are the hematopoietic cells and adipocytes necrosis and a possible concomitant interstitial marrow edema. Though osteocyte necrosis is visible after approximately 2 to 3 hours of anoxia, histological signs of osteocyte death take approximately 24 to 72 hours following oxygen deprivation to appear (Bauer TW; Stulberg BN) [4, 34].
Reactive hyperemia and capillary revascularization occurs to some extent in the periphery of the necrotic zone, and the entry of blood vessels propagates a repair process in which both bone resorption and production incompletely replace dead bone with living bone (Aaron RK) [1]. Dead bone is partially resorbed and new living bone is laminated onto dead trabeculae. Because bone resorption exceeds formation in the subchondral trabeculae, there is a net removal of bone, loss of structural integrity of trabeculae, subchondral fracture, and joint incongruity (Brown TD) [9].
The best evidence suggests a common pathophysiological pathway with compromised subchondral microcirculation (Aaron RK) [1]. A decrease in blood flow of 60% would be expected to reduce the intraosseous pO_2 from 75 to 50 mmHg, assuming a constant oxygen consumption rate (Kiaer T) [21]. This reduction will result in marked ischemia. Three pathogenic mechanisms can lead to decreased femoral head blood flow: vascular

interruption by fractures or dislocation, intravascular occlusion from thrombi or embolic fat, or intraosseous extravascular compression from lipocyte hypertrophy or Gaucher cells. Though a fourth mechanism, extraosseous venous obstruction, has been experimentally shown to have the same effect, it probably has limited clinical significance. Researchers have focused on elevated intraosseous pressure as a pathogenic mechanism in ON and literature related to this increase has recently been reviewed. Elevated intraosseous pressures have been measured within ON femoral heads associated with venous outflow obstruction and venous stasis (Shah KN) [32].

There are a number of pathogenic mechanisms which may result in ischemia and ON:
1. Intracapsular fractures of the femoral neck can cause direct trauma to vessels that supply the subchondral bone, and relatively high incidences of ONFH have been reported in patients with these fractures.
2. An interruption in the vascular flow to the femur head may be secondary to an endoluminal obstruction. A diverse group of etiologies may cause this obstruction, especially, sickle cell aggregations or clots or lipid thrombi. Low oxygen tension environments are hypothesized to trigger haemoglobin precipitation in these patients which leads to erythrocyte sickling. As the patient's age increased, the rate of ONFH was noted to increase; presumably, this was a direct result of repeated vascular insults from which these patients suffered over the course of their lives. Also coagulation factor aberrations have been observed in ONFH: genetic defects, resulting in hypofibrinolysis or thrombophilia, may lead to increased thrombi formation and a subsequent impaired blood flow in the osseous circulation.
Nevertheless, using a case-control methodology, elevated coagulation factor levels have been reported in patients with ON showing absence of known genetic defects.
3. Though it is not a consistently recordable event, the elevations in pressure, within the intraosseous extravascular space, have already been observed to lead to a decrease in the blood flow in those small vessels passing through it.
Many times the increase in extravascular pressure is associated with corticosteroid or alcohol intake has been hypothesized to create an obstruction for arterial inflow or venous outflow; this can lead to ischemia of the marrow elements and osteocytes in the femoral head. Corticosteroids are used to treat a variety of disease conditions including systemic lupus erythematosus, vasculitis, rheumatoid arthritis, asthma, organ transplantation (Aaron RK) [1]. Alcohol abuse has also been correlated to ONFH cases. Also, Gaucher disease has been linked to the development of ON of the femoral head owing to its role in decreasing the capillary blood flow, potentially by increasing the pressures in the intraosseous extravascular space (Schroer WC) [30].
Many other dyscrasias and clinical presentations, like hyperlipidemia, hyperuricemia, pancreatitis, leukemia or lymphoma, hypertriglyceridemia, have been considered as potential causes of ON of the femoral head. Osteonecrosis occurrences have also been reported in those undergoing radiation, bone marrow transplantation procedures, patients suffering from disseminated metastatic malignancies as well as pregnant patients (Aaron RK) [1].
Dysbaric ON presentation is well-characterized by now since safe work in underwater/compressed-air pressure environment, has already been established thanks to a clear approach to specific diving decompression schedules (Uguen M) [37].

CLINICAL PRESENTATION (summary)

To ensure optimal treatment of ON, early diagnosis is necessary since treatment success is related to the stage at which the care is initiated (Hungerford DS) [18].
Very considerable in number are the procedures capable to detect and stage an ON presentation: histological studies, scintigraphy, bone functional evaluations, radiography and/or magnetic resonance imaging (MRI) or computer-assisted tomography (TC), can be considered the most current diagnostic methods available for that aim. ON is usually asymptomatic, at its very early stage, even if patients may develop pain that can be knee, and/or ipsilateral buttock, radiated. Patients typically present a limited range of motion at the hip and suffering from stabbing pain, especially at a forced internal rotation. A detailed interview can identify if any eventual associated risk factor can be evicted through the patient's medical history. ON must be suspected when a patient presents with pain in the hips, shows negative plain radiographs, and no risk factor at anamnesis data; plain radiographs may often appear as normal in the early stages of necrosis. Patients who have had a history of necrosis must be observed for bilateral ON; bilaterality has been reported in up to 70% of observations (Boettcher WG) [7]. Usually the classifications used in the diagnosis of ON include the Ficat and Arlet and the Steinberg University of Pennsylvania systems. Ficat classification, based on standard radiograph presentations, consists of: Stage I, normal imaging. Stage II indicates a normal contour, but there is evidence of bone-remodeling. Stage III is characterized by the evidence of a subchondral collapse, or a flattening of the FH. Stage

IV indicates a tight narrowing of the joint space, with secondary degenerative changes in the acetabulum. Ficat classification system definitely relies on radiographic imaging and therefore the lesion size cannot be quantified, making it impossible 'de facto' to get a real measure of the disease progression. Steinberg expands the Ficat system into six stages and includes quantification of involvement of the FH, within stage 1-5, with three further subsets each: defining mild (less than 15% radiographic involvement of the head's articular surface), moderate (15%-30% involvement of the head's articular surface), and severe (greater than 30% involvement of the head's articular surface) stages. The Association Research Circulation Osseous (ARCO) recommended to shift towards a new classification system, based on the comparation of different procedure findings: radiographic, MRI, bone scan and histologic findings (Amanatullah DF) [3]. However, Ficat and ARCO classifications systems, apparently, are still not reliable enough to assess ONFH occurrence (Schmitt-Sody M) [31].

Currently, ON is diagnosed by a plain AP and frog-leg lateral radiographs of the hip, followed by MRI; but, MRI is considered the most accurate benchmark.

Rarely other tools for assessing an ON presentation could include bone-marrow pressure measurements, venography, and core biopsy.

STANDARD MANAGEMENT (summary) and outcome (HBO_2 excluded)

Treatment options are pharmacologic agents, biophysical treatments, as well as joint-preserving and joint replacing surgeries. An articulated medical management of AVascular Necrosis has been increasingly used during the early stages in an attempt to hinder the progression of the disease.

Lipid lowering agents, anticoagulants, vasoactive substances, and bisphosphonates can all be used to pharmacologically manage AVN. Increases in both the number and size of circulating fat cells have been correlated with the development of ON of the hip; therefore, lipid lowering agents, such as statins, are advantageous due to their capability to reduce the rate of adipogenesis. Statins have been demonstrated to have a protective effect on patients receiving steroids (Pritchett JW) [28]. Anticoagulants such as enoxaparin act via platelet-aggregation inhibition, thus increasing blood flow to ischemic areas of the bone. In those patients with underlying coagulopathy disorders, such as thrombophilia or hypofibrinolysis, these agents are most significantly beneficial. Prostacyclin is a vasoactive agent that improves blood flow, an effect mediated through its vasodilator potential at the terminal vessel level. Even if prostacyclin has shown significant improvement in both clinical and radiologic outcomes of early-stage AVN, possible long-term benefits are still under evaluation.

Bisphosphonates significantly decrease the incidence of collapse of the FH in osteonecrotic hips thanks to an evident limitation in the osteoclast activity. Alendronate has been utilized as an adjunctive therapy at some procedures and has been found to reduce pain and the risk of collapse in early stages of ONFH as well as with hyperbaric oxygen (HBO_2) therapy. Evidence of its utility for the prevention of Total Hip Replacement (THR) and reduction of AVN progression still remains debated (Camporesi EM; Freiberger JJ) [10, 11; 15].

Among the biophysical treatments for ONFH to be considered, we can include the extracorporeal shockwave therapy (ESWT), pulse electromagnetic therapy, and HBO_2 therapy. ESWT has been demonstrated to restore tissue oxygenation, reduce edema, and induce angiogenesis (Reis ND) [29]; ESWT can potentially offer a feasible and good substitute to those other invasive therapeutic modalities actually existing for FH necrosis at its different stages. Though not as widely used, pulse electromagnetic therapy is thought to function by stimulating osteogenesis and angiogenesis; however, its role as early stage ON treatment still remains to be established. A conservative treatment of AVN may be effective, especially in the earlier stages of the disease; though a medical management is capable of improving a better pain control, compliance, and functional outcomes, randomized clinical trials (RCT) with long-term follow up are necessary to determine the effectiveness of therapy (Boettcher WG) [7]. Surgical treatments are not included in this review.

RATIONALE FOR HBO_2 USE:

The actual world literature, lacking in a level 1 of evidence on such a topic, does not allow to identify either the optimal treatment protocol which to adhere to, in the case-management of those patients suffering for a pre-collapse stage of an AVNFH occurrence, or which the early intervention to adopt, so to avoid the bone collapse, getting those desirable outcomes the joint preserving procedures are aimed to.

Among all those possible and feasible therapies, that may effectively gain time granting a delay in the requirement of a hip arthroplasty, we do believe HBO_2 therapy may show a beneficial effect without the invasiveness of a surgical approach.

HBO_2 increases extracellular oxygen concentration and reduces cellular ischemia and edema by inducing vasoconstriction. Studies have reported radiographic improvement in AVN at the stage I according to Steinberg

classification, as well as better pain control and compliance, and range of motion (ROM) improvement, in ON at Ficat stage I-II (Camporesi EM) [10, 11].
Effects of HBO_2 include reduced bone marrow pressure, and increased oxygen delivery to ischemic cells, thus relieving the compartment syndrome and preventing from further necrosis.
A significant pain relief is induced by a decrease in the bone marrow pressure; hyperbaric oxygen therapy stimulates angiogenesis and oxygen dependent cells: osteoclast and osteoblast function for remodelling and repair. It also stimulates multi potential fibroblasts in the bone marrow so to become osteogenic and capable to form bone (Camporesi EM; Thom SR) [10, 11; 35].

ANIMAL STUDY (IF ANY)

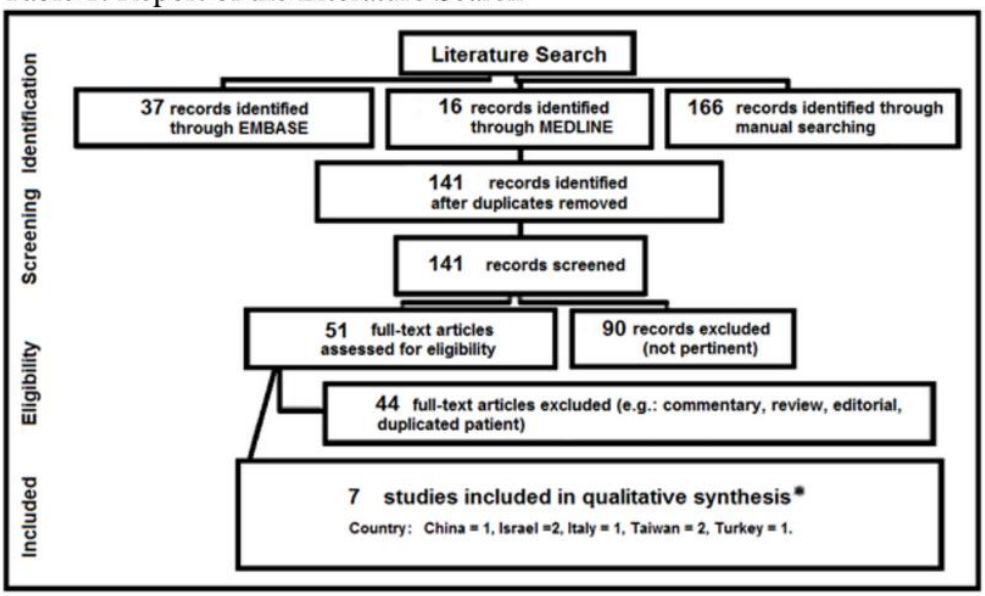
With regard to the controversy about the opportunity or not of a clinical use of hyperbaric oxygen treatment, to stimulate both fracture healing and bone regeneration, animal results (studies upon rats) suggest that hyperoxygenation-mediated relief of ischemia enhances fibroblastic, angioblastic, osteoblastic, and osteoclastic activities up to realize an accelerated complete recovery of rats' femoral head necrosis.
Kataoka et al. study [1992, in spontaneously hypertensive rats (SHR)], was initially oriented to investigate the effects of hyperbaric oxygenation on an ischemic osteonecrosis event and on the ossification disturbance of the femoral heads growth. Authors concluded that HBO_2 prevented both the osteonecrosis and the ossification disturbance of the femoral heads (Kataoka) [20].
Later (1999) it has been measured the grade of healing from a vascular deprivation-induced necrosis of the femoral head in rats exposed to hyperbaric oxygen environment, comparing that with the recovery in the untreated ones. The experimental evidence was that newly formed appositional and intramembranous bone was more abundant in the femoral heads of the hyperbaric oxygen-treated as well as the remodelling phase was more advanced in the rats belonging to the treated group; it was also noted a smaller amount of necrotic debris in the femoral heads of the treated rats. There were no observational differences, on the contrary, as per the severity of the degenerative changes in the articular cartilage and, moreover, the exposure of rats to hyperbaric oxygen does not seem capable to preserve tissue viability after a complete exclusion of all those arteries supplying the femoral head. It appears that it be that tissue increased oxygen availability, higher tension in O_2, the perfect starter in providing optimal settings for reparative processes (Levin D) [23].

Many are the therapeutic options that have already been evaluated in studies on animals suffering for ONFH, various in number and modality so to attempt to meet those equally varied causes of ONFH lesions in animals, based on the possible etiologic and pathogenic mechanisms in them. It has been studied:
1. Exposure to hyperbaric oxygen.
2. Exposure to hyperbaric oxygen and non-weight bearing on the operated hip.
3. Medication with enoxaparin.
4. Reduction of intraosseous hypertension, thanks to a core-decompression procedure, namely drilling a channel through the femoral head.
5. Medication with vascular endothelial growth factor so to accelerate a local revascularization.
6. Medication with zoledronic acid to decrease osteoclastic productivity, and slowing FH remodelling-phase down.

Glucocorticoid-related osteonecrosis shows itself as apoptosis-related, or even depending, therefore differing from the vessel-deprivation-induced tissue-coagulation, as usually found in the idiopathic presentation of osteonecrosis. In the glucocorticoid-treated osteoblasts, the quantities of both alpha-TNF and RANK-ligand and osteoprotegerin are upregulated, freezing the osteoclast differentiation.
Nevertheless it has been observed that a long period under glucocorticoid medication leads to apoptotic behaviour in the osteoblasts and osteocytes of the femoral cortex (Bejar J) [6].
Particular mention to the role of the hyperbaric oxygenation in the treatment of vascular deprivation-induced osteonecrosis of the femoral head when HBO_2 is paired to a non-weight bearing (NWB) approach: in rats it has been observed to induce the preservation of the femoral heads as well as the HBO_2-treated animals demonstrated a well-regenerated hematopoietic tissue. The decrease in the tendency to FH deformation in the HBO_2-treated group might be a reliable predictor of a general better function of the hip joint (Peskin B) [27].

EVIDENCE – BASED REVIEW OF HBO_2 USE

Table 1. Report of the Literature Search



Low level evidence in 4 out of the 7 studies analysed vs.
Moderate or high level evidence in 3 out of the 7 studies analyzed, and in detail as it follows:
- Moderate in a retrospective cohort study, in spite of some bias due to the study itself
- Good in a long-time follow-up numerous case series
- High in a RCT

PROs and CONs:
1 study shows to be neutral as per HBO_2 use
4 studies lightly favour HBO_2 use
2 studies favour HBO_2 use

PATIENTS SELECTION FOR HBO_2

The use of HBO_2 therapy when treating osteonecrosis of the femur head has now shifted from a mere clinical-evidence and inspirational vision to an evidence-supported treatment option. In fact, HBO_2 therapy has been documented to have a success rate of 81% at 7-year follow-up as compared to only 17% for patients in the control group (Reis ND) [(29)]. There are numerous physiological and/or pharmacological benefits to HBO_2 therapy: reduction in the oedematous component of a lesion, better tissue oxygenation, and the possibility of restoring a venous drainage both recovering the affected bone district (due to a progressive and sharp decrease in the intraosseous pressure) and improving local microcirculation (thanks to an increased angiogenesis).
While there is no significance in the hypothesized joint effect of alendronate and hyperbaric oxygen over ESWT in the literature, there is moderate to strong evidence that HBO_2 therapy is a feasible and efficient treatment modality for Ficat stage I-II FHN and in the earliest stages of hip necrosis, especially when applied with adjunctive fenestration drilling or other intervention of core decompression.

CURRENT PROTOCOL:

In Italy the ONFH is included in the accepted indication with: 1Tx/day, 5-6 days/week, ≥ 60 minutes FiO_2=1, 60÷90 Tx at an average bathymetry in the range 2.2÷2.5 ATA. Also the total number of treatment applied to these cases (60÷90 Tx according to the Italian GuideLines to HBO_2 Therapy) appears to be very close to Tx gross average in those studies we analyzed: ≈ 70 Tx.

COST IMPACT

Considering the average price/Tx usually applied in Italy as ≈ 100.$\underline{00}$ €/Tx, the average cost per patient appears to be about 8÷9K euros or ≈ 5,700.$\underline{00}$÷6,400.$\underline{00}$ GBP. This cost appears reasonable if we compared the amount to the direct and indirect costs related to one/more THA interventional procedures.

CONCLUSION : RECOMMENDATION

"**we recommend**":

- daily treatment of ≥ 60 minutes at FiO_2=1 (5 to 6 days a week, and 4-5 weeks per cycle) at 2.4 ± 2.5 ATA, at the initial stage of FHN

[Type 2 recommendation; Level B evidence]

- 60-90 HBO_2 Tx at the initial stage of FHN

[Type 3 recommendation; Level C evidence]

"**we suggest**"

- to schedule MRI and orthopaedic clinical evaluation at 3-4 weeks from the end of the HBO_2 cycle

[Type 2 recommendation; Level C evidence]

"**it could be reasonable**"

- in the meantime apply all those adjuvant resources that could accelerate the recovery, and mainly:

- Minimize weight-bearing (crutch adequate as per height, and contralateral to the lesion),
- Suggesting to ameliorate the BodyMass Index in the case,
- Physical therapies where applicable,
- Quit smoking so not to reduce the efficacy of the treatment.

[Type 1 recommendation; Level C evidence]

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