*AUS DEM LEHRSTUHL*

*FÜR ORTHOPÄDIE*

*PROF. DR. MED. DR. H.C. J. GRIFKA*

DER FAKULTÄT FÜR MEDIZIN

DER UNIVERSITÄT REGENSBURG

# *OSTEONECROSIS OF THE FEMORAL HEAD – A RETROSPECTIVE TRIAL OF JOINT PRESERVING TREATMENT OPTIONS AND A PROSPECT TO FUTURE CLINICAL POSSIBILITIES*

Inaugural – Dissertation

zur Erlangung des Doktorgrades

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## Zusammenfassung in deutscher Sprache

**Die Hüftkopfnekrose – eine retrospektive Auswertung gelenkerhaltender Therapiemöglichkeiten und ein Ausblick auf zukünftige klinische Möglichkeiten**

**Einleitung:**

Die hier vorliegende Arbeit zur aseptischen Hüftkopfnekrose des Erwachsenen gliedert sich im Wesentlichen in zwei große Teile. Im ersten Teil wird ein umfangreicher und vollständiger Überblick über die aktuellsten klinischen und wissenschaftlichen Erkenntnisse zur Ätiologie, Diagnostik und Therapie in der gängigen Fachliteratur gegeben.
Im zweiten Teil, welcher sich wiederum in drei Abschnitte, gliedert werden die selbst angestellten klinischen und wissenschaftlichen Untersuchungen, sowie deren Ergebnisse präsentiert.

Die Femurkopfnekrose ist eine Erkrankung, welche vor allem jüngere Menschen, zwischen 30 und 50 Jahren und somit in Mitten ihrer größten Leistungsfähigkeit betrifft. Dies hat nicht nur für jeden Betroffenen individuell belastende und einschränkende Auswirkungen, sondern ist auch für die Gesellschaft und das Gesundheitssystem eine enorme Belastung [1] [2]. Die aseptische Nekrose des Hüftkopfes beginnt langsam und verläuft unbehandelt progredient bis zur vollständigen arthrotischen Zerstörung des Gelenkes. Die Patienten berichten in vielen Fällen über eine zunehmende diffuse Schmerzhaftigkeit und Bewegungseinschränkung des betroffenen Hüftgelenkes [3]. Die treffende Diagnose wird oft erst spät und somit in bereits fortgeschrittenen Stadien gestellt. Den diagnostischen Goldstandard stellt die Magnetresonanztomographie (MRT) dar. Mittels MRT können bereits die Frühformen der Osteonekrose erkannt werden, wenn das normale Röntgenbild noch völlig unauffällig erscheint [4].
Es haben sich verschiedene Stadien-Klassifikationen der Hüftkopfnekrose entwickelt. Die weitaus geläufigste ist hierbei diejenige der „Association Research Circulation Osseous" (ARCO). Diese berücksichtigt vor allem radiologische Aspekte. Sie ermöglicht eine Einteilung in die Stadien I bis IV, wobei im potentiell reversiblen Stadium I nur im MRT pathologische Veränderungen sichtbar sind. Im Stadium ARCO II wird auch das normale

Röntgen positiv, mit vermehrter Sklerosierung des Nekroseareals, bei jedoch völlig erhaltener Hüftkopfkontur. Im Stadium III kommt es zu subchondralen Einbrüchen, welche sich im Röntgenbild als eine Entrundung des Hüftkopfes darstellen. Das finale Stadium IV stellt die vollständige Zerstörung des Gelenkpartners dar [5] [6]. Diese Einteilung ist neben dem akademischen Interesse vor allem für die Therapie von höchster Relevanz.

Obwohl viele Risikofaktoren bekannt sind, ist die exakte Ätiologie der Erkrankung noch unklar. Als mögliche Risikofaktoren gelten neben den „Lifestyle-Faktoren" Rauchen und Alkoholabusus, vor allem eine längere oder höher dosierte Therapie mit Kortikosteroiden. Desweiteren werden physische Überlastung mit Mikrotraumata, metabolische Erkrankungen, wie der Morbus Gaucher und genetische Vorerkrankungen, wie die Sichelzellanämie oder Thrombophilien genannt [7] [8].

Pathomechanismus:

Der Pathomechanismus der Hüftkopfnekrose war lange Zeit unklar, jedoch scheint sich mittlerweile die Theorie eines erhöhten intra-ossären Druckes zu bestätigen [9] [1]. Dabei wird davon ausgegangen, dass im erkrankten Femurkopf der intramedulläre Druck gesteigert ist. Dies führt zu einer Kompression und in Folge dessen zu einer Obstruktion von kleinsten venösen Gefäßen. Dadurch kommt es zu einem gestörten Abfluss des Blutes und somit zu einem erhöhten Blutvolumen im Knochenmark. Dies führt wiederum zu einer Steigerung des Druckes im spongiösen Knochen. Dieser circulus vitiosus bedingt eine Minderversorgung des Knochenmarks mit Sauerstoff und endet letztlich im nekrotischen Untergang des Gewebes [10].

Hintergrund:

Aus der Pathogenese ergeben sich auch die geläufigsten gelenkerhaltenden Therapien. Diese haben als primäre Grundidee den Versuch der Entlastung des gestauten Kompartiments, da man sich dadurch eine Normalisierung des Blutflusses und folglich eine Regeneration des Gewebes erhofft. Bei erhöhtem intrakompartimentellem Druck erfolgt somit nach Ficat und Arlet eine Core Decompression [9]. Das primäre Ziel aller Therapieversuche ist in frühen Stadien immer die Erhaltung des Hüftgelenkes. Dies sollte wenn möglich dauerhaft sein, jedoch sollte dadurch zumindest Zeit gewonnen werden, bis die Implantation einer Totalendoprothese (TEP) nötig wird. Als mögliche konservative Therapieoption wird vor allem die Entlastung des betroffenen Gelenkes mittels Gehstützen empfohlen, um in der akuten Phase eine weitere Eskalation zu fortgeschrittenen Stadien zu vermeiden [5]. Ob eine spontane Remission, allein dadurch zustande kommt ist unklar. Auch vielfältige medikamentöse Therapiemöglichkeiten von Statinen, über Bisphosphonate, bis hin zu Rheologika, wie das stabile Prostazyklin-Analogon Ilomedin werden in der klinischen Praxis eingesetzt. Durch das am häufigsten angewandte und am besten erforschte Ilomedin erhofft man sich eine Steigerung des intramedullären Blutflusses, mit einer konsekutiven Regeneration des Knochengewebes. Ilomedin wird intravenös in einem fünf tägigen Schema mit ansteigender patientenadaptierter Dosis verabreicht [11]. Es konnte gezeigt werden, dass Patienten, welchen das Medikament in den frühen ARCO Stadien I und II verabreicht wurde, eine deutliche Reduktion der Schmerzen, eine Zunahme der Mobilität und sogar eine radiologische Verbesserung zeigten [12]. Ein großer Vorteil dieser Therapie ist die fehlende Invasivität und ihre relativ geringen Nebenwirkungen.

Als operative gelenkerhaltende Therapie ist die sogenannte „Core Decompression“ am weitesten verbreitet und auch am besten untersucht. Hierbei handelt es sich um eine Anbohrung des Hüftkopfes, mit dem Ziel der Druckentlastung [13]. Daneben soll durch das bewusste Verursachen einer intramedullären Blutung ein Regenerationsreiz gesetzt werden. Die Anbohrung erfolgt meistens mittels Kirschnerdrähte, welche unter Bildwandlerkontrolle in das nekrotische Areal eingebracht werden. Klassischerweise wird die Nekrose fächerförmig angebohrt, um einen größeren Anteil des defekten Bereiches zu erfassen [14]. Neben der Anbohrung mit K-Drähten kann dafür auch eine etwa zehn Millimeter starke Hohlfräße verwendet werden [15]. Dies eröffnet die Möglichkeit das nekrotische Material direkt zu entfernen und bei einer autologen Spongiosaplastik durch andernorts gewonnene intakte Spongiosa zu ersetzen [16]. Der Nachteil hierbei ist jedoch der größere kortikale Defekt und die damit verbundene Schwächung und Frakturgefährdung des Schenkelhalses. Dieses Risiko wird jedoch durch eine postoperative Ent- oder Teilbelastung minimiert. Jedoch ist der Eingriff mit einem größeren Aufwand verbunden, da hierfür ein zweiter OP-Situs (Beckenkamm) geschaffen werden muss. Durch die in der gesunden, durchbluteten Spongiosa enthaltenen Osteoprogenitor Zellen erwartet man sich einen zusätzlichen Wachstums- und Heilungsstimulus. In der Literatur werden auch weitere autologe Knochentransplantate, wie gefäßgestielte Fibula-Transplantate beschrieben [17]. Diese konnten sich aber nicht in der breiten Anwendung durchsetzen. Als weitere gelenkerhaltende Therapie sind Umstellungsosteotomien zu nennen. Diese sind jedoch auf Grund der Komplexizität des Eingriffes und der geringen Patientenakzeptanz eher von untergeordneter Bedeutung und speziellen Ausnahmen vorbehalten. Als letzte Therapiemöglichkeit bei weit fortgeschrittener Nekrose oder bei Versagen der gelenkerhaltenden Optionen bleibt die Hüftgelenkstotalendoprothese (Hüft-TEP) [18]. Diese stellt eine sehr gute Therapieform dar, ist bei den überwiegend jungen Patienten mit Femurkopfnekrose jedoch so lange wie möglich hinaus zu zögern, um perspektivisch häufige Wechsel- und Revisionseingriffe zu vermeiden.

**Hauptteil**

Im zweiten Abschnitt der hier vorliegenden Arbeit werden die selbst durchgeführten Untersuchungen und Auswertungen dargelegt. Dieser Abschnitt gliedert sich wiederum in drei Fragestellungen. Zum ersten wird ein retrospektiver klinischer Vergleich zwischen der Anbohrung und der Anbohrung mit autologer Spongiosaplastik angestellt.

In der zweiten Fragestellung wird die Zielgenauigkeit der beiden Therapievarianten untersucht.

Im dritten Abschnitt erfolgt die Vorstellung einer bisher so noch nicht beschriebenen Darstellung der intramedullären Perfusion des Hüftkopfes mittels MRT-basierter Perfusionsmessung.

Da in der Literatur viele verschiedene Konzepte zur gelenkerhaltenden Therapie bei Hüftkopfnekrose beschrieben werden, soll im ersten Teil der vorliegenden Arbeit ein Vergleich zwischen der konventionellen Hüftkopfanbohrung und der Anbohrung mit autologer Spongiosaplastik gemacht werden.

In einem retrospektiven Studiendesign wurden Patienten, welche im orthopädischen Universitätsklinikum Bad Abbach gelenkerhaltend therapiert worden waren, nachuntersucht. Hierfür wurden aus einem Gesamtkollektiv von 289 Hüften mit der Diagnose Hüftkopfnekrose aus dem Zeitraum von 2006 bis 2012 die 62 Fälle mit einer gelenkerhaltenden Therapie ausgewählt. Davon konnten 31 Fälle für die Nachuntersuchung rekrutiert werden und für die folgenden Untersuchungen eingeschlossen werden.

Die Nachuntersuchung setzte sich zusammen aus einer klinischen Untersuchung, mit Ermittlung der Bewegungsfähigkeit (range of motion, ROM), eventuellen Kontrakturen und Feststellung der Schmerzhaftigkeit in Ruhe und unter Belastung mittels der visuellen Analogskala (VAS 10). Ergänzend wurden die Patienten gebeten einige Fragebögen und

Scores zu beantworten. Hierbei kamen der Harris Hip Score (HHS), der Hip disability and Osteoarthritis Outcome Score (HOOS), der EuroQol-5D (EQ-5D) und der Short Form 36 (SF-36) zum Einsatz. Für die radiologische Beurteilung des Hüftgelenkes wurde ein konventionelles Röntgen in Hüftübersicht und in der Lauenstein-Projektion angefertigt. Hierauf wurde bei allen Patienten eine Magnetresonanztomographie (MRT) mit Kontrastmittel durchgeführt. An Hand dieser Daten erfolgte eine Gegenüberstellung von jeweils elf Patienten mit Anbohrung oder Anbohrung mit Spongiosaplastik. Diese relativ kleine Anzahl an Studienteilnehmern in dieser Subgruppe war vor allem durch den Versuch der bestmöglichen Vergleichbarkeit begründet, da durch „matched pairs“ eine möglichst homogene Verteilung der Gruppen erreicht werden sollte. Das „matching“ erfolgte nach den Parametern Geschlecht und Alter. Außerdem wurden in jeder Gruppe nur Patienten berücksichtigt, welche von dem jeweils gleichen Operateur behandelt worden waren. Zusätzlich lag bei allen Eingeschlossenen ein initiales ARCO II Stadium vor. Die Nachuntersuchung erfolgte im Mittel etwa vier Jahre nach der Intervention in der Gruppe der „Core Decompression“ und etwa fünf Jahre nach Therapie bei den Patienten die eine autologe Spongiosaplastik erhalten hatten.

**Vergleich zwischen Core Decompression und autologer Spongiosaplastik**

Die Analyse der Daten erbrachte zwar keine statistisch signifikanten Unterschiede bezüglich der klinischen und radiologischen Ergebnisse zwischen den beiden Gruppen, jedoch generell gute Langzeitergebnisse mit hoher Patientenzufriedenheit. In den klinischen Auswertungen des Bewegungsausmaßes der behandelten Hüfte, als Indikator für die Funktionalität des Gelenkes und der Schmerzhaftigkeit während Belastung, erzielten die Patienten mit einer autologen Spongiosaplastik etwas bessere Ergebnisse. Dies spiegelte sich auch in den Angaben der Fragebögen wieder. Dort gaben Patienten nach autologer Spongiosaplastik etwas bessere hüftspezifische Werte an. Allerdings war das Abschneiden in der Gruppe der reinen Anbohrung etwas besser in Hinblick auf die Einschätzung der generellen und psychischen Gesundheit. In der radiologischen Beurteilung, also einer erneuten Stadieneinteilung waren im Durchschnitt keine Unterschiede feststellbar. Dies bedeutet, dass beide Therapieformen sowohl im klinischen, als auch im subjektiven und im radiologischen Outcome sehr ähnlich waren. Dies spricht wiederum für die Gleichwertigkeit beider Therapie Optionen.

**Zielgenauigkeit**

Der zweite Aspekt dieser Arbeit beschäftigt sich mit einer relativ neuen technischen Möglichkeit, welche zunehmend Einzug in die operative Medizin erhält. Es geht hierbei um die dreidimensionale Rekonstruktion anatomischer oder pathologischer Formationen. In der vorliegenden Untersuchung wurden bei 22 angebohrten Hüften die Nekrose und der Bohrkanal dreidimensional aus den MRT-Aufnahmen rekonstruiert. Aus der Rekonstruktion erfolgte eine Vermessung der Ausmaße und der Volumina der nekrotischen Areale. Danach wurden die Abweichungen der jeweiligen Bohrkanäle vom Mittelpunkt der Nekrose für jede einzelne Raumachse ausgemessen. Es erfolgte eine Gegenüberstellung von zehn Hüften mit reiner Core Decompression gegen 12 Hüften mit Spongiosaplastik. Aus den gewonnenen Ergebnissen zeigte sich, dass alle nekrotischen Areale von der Anbohrung getroffen wurden. Ein Vergleich der Genauigkeit der Intervention zwischen der klassischen Anbohrung und der Anbohrung mit anschließender Spongiosaplastik ergab keine statistisch signifikanten Unterschiede zwischen den beiden Methoden.

Im Zuge der Volumenbestimmung der Nekrose konnte der bereits in der Literatur beschriebene Zusammenhang zwischen größerem Ausmaß der Nekrose und einer wahrscheinlicheren Progredienz der Erkrankung bestätigt werden.

**Intramedulläre Perfusionsmessung**

Im dritten Teil dieser Studie wurde das neuartige Verfahren der intramedullären Perfusionsmessung untersucht. Das Grundprinzip dieser Methode beruht auf MRT-Aufnahmen zu bestimmten Zeitintervallen nach Kontrastmittelapplikation. Hierfür wurde den Patienten ein Kontrastmittel injiziert und nach festen Zeiten wurden bestimmte MRT-Sequenzen durchgeführt. Die Idee hinter dieser Methode besagt, dass sich die Kontrastmittelanreicherung im Knochenmark proportional zur Durchblutung verhält. Das heißt, dass sich aus der Signalsteigerung im MRT Rückschlüsse auf die Perfusion ziehen lassen müssten. Dieser Abschnitt der Studie wurde als rein deskriptiver Versuch zur Anwendbarkeit dieser neuartigen und bisher kaum beschriebenen Methode durchgeführt. Dies konnte an 26 der behandelten Hüften erfolgen, unabhängig von der Art der Therapie oder dem initialen Stadium. Ergänzend wurden auch die gesunden, beziehungsweise unbehandelten Hüften betrachtet. Es ließ sich erkennen, dass Patienten mit einer Ilomedin-Infusionstherapie erhöhte Perfusionswerte aufwiesen. Die Bedeutung und Zusammenhänge dieser Ergebnisse müssen in weiteren Untersuchungen ebenso dargelegt werden, wie die Möglichkeit durch die Perfusionsmessung noch früher Hinweise auf eine Störung in der intramedullären Perfusion zu bekommen und damit eine Risikoabschätzung für das Auftreten einer avaskulären Knochennekrose.

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## 1.1 Osteonecrosis of the femoral head (ONFH)

Osteonecrosis of the femoral head (ONFH) is a progressive locally limited disease, due to a reduced blood flow in the affected area. The impaired perfusion leads to a gradual destruction of the femoral head and thus to an enormous effect on the patient's lifestyle [18]. As there are mostly younger people in the third to fifth decade affected, they are forced to change their work and leisure activities [2] [19]. In most cases the necrosis is restricted to the weight bearing area of the femoral head. Normally the disease starts unnoticed without any pain, but as it progresses most patients suffer from an enormous pain during weight bearing and in progressed stages also at rest [20]. Untreated the avascular necrosis leads to secondary arthrosis of the hip and to the necessity of total hip replacement [21] [22]. The natural course of the disease leads within two or three years to a complete joint destruction and in consequence to total hip replacement [23].

Synonyms are avascular or aseptic necrosis of the femoral head (AVN).

It is also possible to distinguish between idiopathic or secondary necrosis. In case of secondary necrosis there can be found causes like trauma, metabolic diseases or medication. For the idiopathic genesis on the other hand there are no evidential trigger factors, although even there can be found certain risk factors [2].

## 1.2 Epidemiology

In Germany there is a reported prevalence of 5,000 to 7,000 new diseases per year [24]. The diagnosis of avascular necrosis of the femoral head accounts for 5 to 12 percent of total hip replacements [2]. With about 10,000 to 20,000 new cases per year only in the USA it is obvious that ONFH is an important factor in health care systems worldwide [20].

In about 50 percent the patients suffer a bilateral involvement and in even 80 percent of steroid induced necrosis there is a bilateral affection [9].

## 1.3 Etiology and risk factors

There is a wide range of different etiological factors for the development of an ONFH. In general it has to be distinguished between a traumatic and a non-traumatic genesis. In traumatic conditions with fracture or dislocation of the femoral head the reduced blood flow, as a result of structural interruption of the blood vessels is obvious. Nevertheless, there are known several risk factors, like steroid medication, alcohol abuse, smoking or metabolic diseases [2] [25] [10].

### 1.3.1 Corticosteroid

A) Distribution

One of the major risk factors is the intake of corticosteroids. Studies showed, that about 10 to 30 percent of osteonecrosis can be associated with steroid medication [2] [21] [26]. However, only in 8 to 12 percent of patients treated with high dose corticosteroids for a longer period appeared signs of osteonecrosis. Felson T. et al. came to the conclusion that "The oral dose effect amounts to a 4 to 6 percent increase in the risk of AVN for every 10 mg/day rise in oral steroids during the first 6 months of therapy" [7]. Other reports cite an elevated risk for AVN at a dose of more than 2 g of steroids within a period of about two months [10] [27].

B) Pathogenesis

It is still unclear how corticosteroid therapy leads to osteonecrosis. One explanation could be a raised intraosseus pressure, which is either caused by a swelling of bone marrow fat cells or fat emboli [28]. The increased pressure causes an obstruction of small femoral vessels with a following ischemia and death of osteocytes [29] [30]. A possible model for increased fat cell content in bone marrow could be that, in vitro, dexamethasone has the competence to induce primary marrow stroma cells to differentiate to adipocytes. As bone cells and fat cells share a common precursor and dexamethasone can induce adipogenesis, it results in a mismatch between bone and fat cells. This may lead to increased intraosseus pressure, venous stasis and decreased arterial perfusion [31].

However, the negative effects of steroid intake are not only attributable to the compromised vascularity, but even more to osteoblasts and osteocytes apoptosis [32] [30] [33]. Within the last years it became obvious that apoptosis of osteocytes and lining cells leads to interruption in the mechanosensory network of the femoral head and thus to a reduced repair mechanism of structural micro damages, followed by collapse of the bone [30]. Glucocorticoids have an effect on all bone cells, even on osteoclasts. They decrease the production of osteoblasts and osteoclasts, increase the apoptosis of osteoblasts and prolong the lifespan of osteoclasts [34]. This process leads to an abnormal bone metabolism and thus to reduced bone mass and decreased stability. The thesis of osteocytes and osteoblast apoptosis as the major pathogenetic factor in steroid induced osteonecrosis is emphasized by the fact that there are not found apoptotic cells in osteonecrosis of other etiology, but only in steroid induced cases [34] [35] [33].

### 1.3.2 Alcohol

Studies showed that about one third of patients with idiopathic ONFH have a history of regular or excessive alcohol intake [36] [37]. The risk seems to be dose related, but it is, nevertheless, difficult to define a harmful quantity. However, it could be seen that an intake of more than 400 ml ethanol per week increases the risk of osteonecrosis 9.8 fold [2] [25]. Although the exact pathomechanism is still not clear, it seems there is a similarity to steroid induced osteonecrosis [25]. Histological surveys on alcohol induced ONFH showed an increase of fat cells and marrow fat and thus a reduction of osteogenetic cells. In addition to that the increased intraosseus fat content leads to elevated intraosseus pressure and thus to venous stasis, diminished blood circulation and finally to ischemic necrosis [3]. Besides, there are found elevated serum lipid peroxides, which have a pro inflammatory effect and induce degeneration of small blood vessels.

This can lead to a reduced bone perfusion, an effect which has also been observed in hepatic steatosis [25] [38].

### 1.3.3 Nicotine

Various surveys showed that smoking is a potential risk factor for osteonecrosis [22]. It is assumed that there is an increased risk for common smokers and a cumulative effect of a minimum of 20 pack years [10]. Exposition to cigarette smoke does affect every human organ system, so it also leads to intramedullary vasoconstriction and in the following to an ischemic necrosis of the bone [1]. Nicotine abuse can decrease osteogenesis, bone volume and vascular reactivity, which may also explain prolonged healing processes. The reduced blood supply and the decline of bone producing and repairing cells lead to a vulnerable tissue and an increased risk for necrosis of the femoral head [39] [10].

### 1.3.4 Physical strain

It seems that hard physical strain does not increase the possibility of ONFH. However, it has an impact on the proceeding of a preexisting AVN. This may be the result of physical stress induced micro lesions, which can worsen the vascular supply of the necrotic bone area [40]. Another reason for strict avoidance of physical strain in patients with osteonecrosis is on the one hand a symptomatic improvement of the pain and on the other hand a reduced number of insufficiency bone fractures [41].

### 1.3.5 Genetic

There seem to be various genetic disorders, connected with avascular necrosis in general and ONFH in particular. Especially patients with sickle cell anemia are confronted with an increased risk of getting ONFH [42]. Approximately about half of patients at the age of 35 are affected [43] [2]. These patients suffer from a higher disposition for an activation of the coagulation system, which can lead to occlusion of small blood vessels and thus to ischemic osteonecrosis [44]. There is also a discussion about other coagulation abnormalities, like Factor V Leiden mutation, thrombophilia or hypofibrinolysis. They lead to increased incidents of blood clots or to a reduced ability to dissolve these clots. It has been shown that up to 82% of patients with ONFH (in contrast to 32% in the control group) had at least one coagulation abnormality [10]. Koo, Lee et all. found that certain genetic polymorphisms in the endothelial nitric oxide synthase (eNOS) gene were frequently present in patients with ONFH. This leads to a reduction of vasodilatative effects and an inhibition of platelet aggregation of eNOS and thus to an impaired blood supply in the femoral head [39]. A deprived vascularization, as it can be found in VEGF-gene polymorphisms, may also be a co-factor for osteonecrosis [45]. Liu, Chen et all. succeeded in finding a genetic mutation in three families with autosomal dominant inheritance. They detected a genetic disorder in the type II collagene, the major structural protein in cartilage [46]. It is hard to decide whether all these genetic disorders are risk factors for themselves or they are just acting as co-factors along with other risk factors. This would explain why some people with a certain risk exposition get sick, whereas others stay healthy. However, the knowledge of the genetic risk is important, because it makes it possible to screen people at an early stage. But this is not yet a clinical standard.

Although there are many different risk factors and the exact pathomechanism is still unclear, it seems quite likely that a disturbed blood supply, an increased intraosseous pressure and abnormal cellular mechanisms lead to impaired nourishment of osseous structures and thereby to an aseptic necrosis of the bone [39] [2].

## 1.4 Clinic

As the clinical course of OFNH is very unspecific and often without any symptoms at the beginning, it is difficult to recognize the disease in an early stage, when there would be good chances for conservative treatments. The first clinical sign is mostly a deep pain in the groin, which may derive from the associated bone marrow edema within the femoral head [11] [47]. In this stadium a reduced range of motion, especially internal rotation and abduction, of the affected hip is already possible [9]. A clicking sound during movement and enormous pain might be a sign for a collapsed femoral head and therefore an advanced stage [2].

## 1.5 Radiological Imaging

As the disease starts in most cases with rather unspecific clinical signs, radiological imaging is very important in early diagnostics. The first step should always be plain radiography, with an anterior-posterior and a frog-leg lateral radiograph [2]. In an early stage of the disease there are no specific signs on the x-ray visible, but it is a good tool to get an overview about the integrity and the constitution of the hip joint [10]. Radiological signs, like cysts, sclerosis, the crescent sign, which derives from subchondral collapsed bone, or complete collapse and destruction of the joint, appear on the plain radiograph months after the onset of pain [47] [2] [5] [4]. As radiography is a tool for advanced stages of ONFH or for the differential diagnosis to arthrotic degenerations of the hip joint, the standard for early diagnosis of ONFH is the magnet resonance imaging (MRI) [48] [49]. With sensitivity and specificity of 99%, MR imaging is the most accurate way for early diagnosis of AVN [2] [5]. A healthy femur shows a high intensity signal, due to the hydrogen rich marrow fat. Invasive processes or displace of the fat, like in necrosis, lead to an altered signal intensity [4]. The MRI of painful hips often shows a bone marrow edema (BME), which appears with low signal intensity in T1-weighted images and high signal intensity in the T2-weighted fat suppressed STIR-MRI (Short-Tau

Inversion Recovery-MRI) [47] [5]. It is not definitely clear if the BME can be seen as a direct precursor of ONFH or just of transient osteoporosis [47] [50]. However, in early stages of osteonecrosis there is often a bone marrow edema visible, which can progress to a higher stage of ONFH, with subchondral micro-fracture, or disappear completely after a certain period of time [5]. Other typical signs of ONFH in MR images, like the double line sign or signal intensity changes, hint at the necrotic lesion. A single density line on the T1 pictures demarcates the normal-ischemic-bone interface, whereas a double density line on T2 weighted images represents the hypervascular granulation tissue, which derives from the healthy bone and is a repair mechanism of the necrotic area [2] [51]. Another advantage of MRI is the 3-dimensional overview about the whole joint, which makes it possible to oversee the exact location and extent of the lesion [51].

Bone scan or szintigraphy is a previously used nuclear medicine method in osteonecrosis diagnostic. Nowadays with high specific MR imaging allowing exact diagnosis of ischemic process in the bone, the use of these methods is not state of the art anymore. The sensitivity of szintigraphy with technetium-99 is only about 60 % with a false negative rate of about 25 to 45% [2] [5]. Mostly in the beginning of the disease these techniques are very unspecific, but in the course of the disease they become more sensitive. The typical increased uptake as a "cold in hot" pattern can also be seen in infectious processes like osteomyelitis or coxitis. With a full-body-scan it is possible to detect multiple osteonecrotic lesions [48].

Also not within standard diagnostic procedures is the computed tomography (CT), although it is a good way to detect a cartilage collapse on an early stage. But its high costs and the enormous radiation load make this technique more or less obsolete [2]. Other diagnostic tools, like intraosseous pressure measurement, venography or biopsy, are not used, because they are very invasive and their sensitivity is not better than MRI [2].

## 1.6 Staging

Osteonecrosis almost always progresses in different stages. These can last interindividually very differently and are, until a certain point, at least theoretically totally reversible [6]. As stage is the most important factor for prognosis and for the chosen treatment, an exact and diagnostically conclusive staging is of great importance [2] [10] [3]. The prognosis is highly related to the extent and location of the necrotic lesion. That is why almost all staging types include this information, beside different clinical or radiological findings [6] [3] [10]. In general, every classification combines clinical signs, like pain or reduced range of motion, and radiological pathologies. The most important radiographic factors are the integrity of the femoral head, whether the bone is pre- or postcollapse. The collapse derives from a mechanical failure of the bone structure. Large lesions can be seen by a contour change of the femoral surface or in advanced course by femoral head depression, known as the “out of round” appearance. The smaller ones are only visible on MRI, by the crescent sign. The larger the collapse, the greater is the risk for necessity of total hip replacement. Another prognostic factor is the size of the lesion and a possible acetabular involvement. Both are crucial for the kind of treatment and the prognosis [10] [9].

Also of great interest is the location of the lesion. There is a difference whether the necrosis is in the weight bearing area or apart from it. In the weight bearing area there is greater mechanical strain, what may lead to early collapse of the damaged tissue. Because of the importance of correct classification there exist many different types of classification.

One of the elder and currently sometimes used in clinical routine is the staging of Ficat and Arlt. They described five different stages, from 0 to IV. Stage 0 is the preclinical and pre-radiological so called “silent hip”, with an increased intramedullar pressure. This diagnosis is only possible if there is a confirmed osteonecrosis of the contralateral hip. Stage I is only clinical signs, with reduced movement and pain in the groin or the thigh, but no radiographic signs. Stage II presents with persistent or increased pain, limited range of motion and first radiographic signs, like sclerosis, cysts or diffuse osteopenia. Stage III of Ficat and Arlt contains subchondral fracture, with the crescent sign and a segmental flattening of the femoral head (“out of round” appearance). The patient suffers from continuing strong pain and limited motion. The loss of articular cartilage, arthritic deformation and a diminished range of motion define stage IV [9] [2].

More commonly used are the classifications of Steinberg (table 1) and of the ARCO (association research circulation osseous) (table 2). The Steinberg classification describes seven stages plus three stages of extent and grades of involvement of the femoral head, whereas the five ARCO stages also take the localization into account. Both classifications combine pathopysiological basics and radiologic imaging [6] [5] [52] [47] [48].

| Stage | Radiograph signs | MRI and bone scan | Extent or grade of involvement |
|---|---|---|---|
| **0** | Normal or non diagnostic | Normal or non diagnostic | Not visible |
| **I** | Normal | Abnormal, changes of marrow or bone cells | A: mild <15%<br>B: moderate 15-30%<br>C: severe >30% |
| **II** | Abnormal, cystic and sclerotic changes | Sclerotic changes, repair mechanism | A: mild <15%<br>B: moderate 15-30%<br>C: severe >30% |
| **III** | Crescent sign due to subchondral collapse | Subchondral micro fractures, crescent sign | A: mild <15%<br>B: moderate 15-30%<br>C: severe >30% |
| **IV** | Flattening of articular surface<br>Depression of femoral head surface | Flattening of articular surface<br>Depression of femoral head surface | A: mild <15%, < 2 mm<br>B: moderate 15-30%, 2-4 mm<br>C: severe >30%, >4 mm |
| **V** | Joint narrowing, with or without acetabular involvement | Joint narrowing, with or without acetabular involvement | A: mild <15%, < 2 mm<br>B: moderate 15-30%, 2-4 mm<br>C: severe >30%, >4 mm |
| **VI** | Advanced degeneration, osteoarthritic deformation | Advanced degeneration, osteoartritic deformation | |

**Table 1: Steinberg classification [44]**

| Stage | Radiograph signs | MRI and Bone scan | Extent or grade of involvement |
|---|---|---|---|
| **0**<br>**(Initial stage)** | Negative | Negative | Not visible |
| **I**<br>**(Early Reversible)** | Negative | Bone marrow edema, diffuse subchondral changes | A: < 15%<br>B: 15-30%<br>C: >30% |
| **II**<br>**(Early irreversible)** | Sclerosis, osteopenia, unspecific | Necrotic lesion, reactive interface "double line sign", "cold in hot" | A: < 15%<br>B: 15-30%<br>C: >30% |
| **III**<br>**(transition stage)** | Subchondral collaps "crescent sign", flattening of femoral head surface, sclerosis | Subchondral fractures "crescent sign", "cold in hot" | A: < 15%, < 2mm flattening<br>B: 15-30%, 2-4mm flattening<br>C: >30%, > 4mm flattening |
| **IV**<br>**(final stage)** | Complete joint destruction, Arthritic signs, joint space narrowing | Joint destruction, arthritic changes, loss of articular cartilage, "cold in hot" | |

**Table 1: ARCO classification [5] [6]**

The ARCO classification is the most common one in clinical routine. In addition to the extent of the lesion, which is described in stages I to III as shown in the table above, there can be indicated a localization  for the stages II and III: A: medial, B: central and C: lateral. This may be of importance, because grad C has the worst prognosis of these three. Although there are five stages (0-IV) in the traditional ARCO classification, there are only four stages (I-IV) in clinical use, because stage 0 is neither clinically nor radiologically visible, but only histologically [5] [6].

Due to numerous different staging systems, without a standard unified classification, and a lack of inter observer reliability, it is very difficult to compare different studies or clinical courses [2] [53].

It is also possible to perform an exact histological staging, as described by Arlet and Durroux in 1973 [9]. But as it is necessary to get tissue by invasive procedure and as the histological findings are not consistent with clinic or radiology, it is not performed anymore.

As another radiological staging parameter the combined necrotic angle of Kerboul has to be mentioned. Although it´s use in clinical routine declined, it is a quite meaningful tool to assess the extent and the prognosis of a necrotic lesion of the femoral head. The combined necrotic angle of Kerboul is determined by adding the necrotic angles in the anterior-posterior and the axial plane of the plain radiograph. First of all the centre of the femoral head has to be defined. Thereafter a sector, which describes the necrotic lesion on the femoral surface, is measured in both projections (see figure 1 below).

The two angles are added. [54] [55]

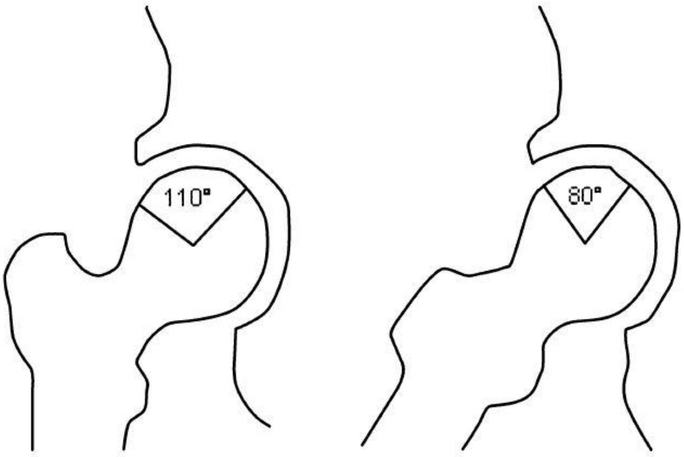


**Figure 1: Schematic depiction of the determination of the Kerboul angle [54]**

A Kerboul angle <200 degrees counts as a small lesion with a rather good prognosis. Angles >200 degrees showed a significant worse outcome after joint preserving therapy [56].

## 1.7 Therapy

As most patients are quite young and naturally the course of untreated osteonecrosis leads to the collapse of the femoral head, joint preserving therapy is necessary. There are many different treatment options; however, none could proof uniformly successful [57].

### 1.7.1 Nonoperative therapy

Table 3 below shows a small excerpt of the literature dealing with conservative treatment opportunities for femoral head necrosis. There is a large amount of studies, most of them about pharmaceutical therapies. The most commonly used drug in clinical routine is the stable prostacyclin analogue Iloprost. There are also some reports about other conservative methods, but not that many. A limitation of most works is the small patient numbers and the rather short follow up times. Figure 2 shows a chronological timeline of the mentioned literature.

| Year | Author | Journal | Title |
|---|---|---|---|
| 2005 | Aigner et al. | Wiener Klinische Wochenschrift | Bone marrow edema syndrome of the femoral head: Treatment with the prostacyclin analogue iloprost An MRI-controlled study |
| 2005 | Disch et al. | Journal of Bone and Joint Surgery | The management of necrosis-associated and idiopathic bone-marrow edema of the proximal femur by intravenous iloprost |
| 2005 | Wang et al. | Journal of Bone and Joint Surgery | Treatment for Osteonecrosis of Femoral Head: Comparison of Extracorporeal Shock Waves with Core Decompression and Bone Grafting |
| 2005 | Meizer et al. | Wiener Klinische Wochenschrift | MRI-controlled analysis of 104 patients with painful bone marrow edema in different joint localizations treated with the prostacyclin analogue iloprost |

| | | | |
|---|---|---|---|
| 2006 | Mont et al. | Journal of Bone and Joint Surgery | Nontraumatic osteonecrosis of the femoral head: Ten years later |
| 2011 | Jäger et al. | International Orthopaedics | Efficiency of iloprost treatment for osseous malperfusion |
| 2011 | Rajpura et al. | Hip International | Medical management of osteonecrosis of the hip: A review |
| 2012 | Beckmann et al. | Rheumatology International | Infusion, core decompression, or infusion following core decompression in the treatment of bone edema syndrome and early avascular osteonecrosis of the femoral head |
| 2015 | Roth et al. | Zeitschrift für Orthopädie und Unfallchirurgie | S3-Leitlinie. Teil 2: Atraumatische Femurkopfnekrose des Erwachsenen – unbehandelter Verlauf und konservative Behandlung |

**Table 3: Literature for conservative treatment options**

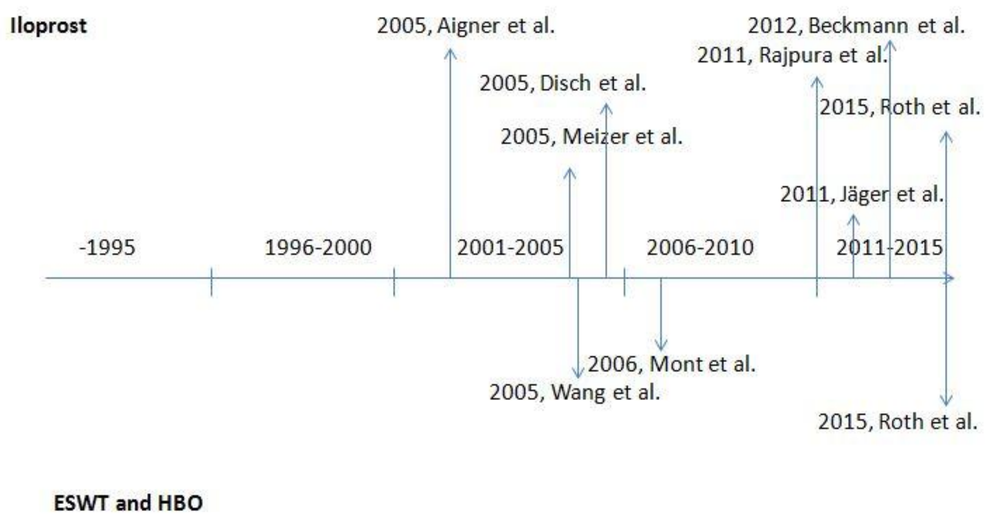


**Figure 2: Literature non operative therapies: Iloprost, Extracorporeal Shockwave Therapy (ESWT) and Hyperbaric Oxygen Treatment (HBO)**

If the disease is diagnosed in an early stage, it is possible to try conservative methods. It is described in literature that early detected small lesions have a chance to recover spontaneously [10]. Because of that it is often recommended to reduce weight bearing of the affected hip by using a cane or crutches [58]. This may slow down the progression of the disease or lead to a normalization of clinical and radiological findings. It is supposed that the collapse of the joint can be caused by trauma related epiphyseal trabecular impaction or by an insufficiency bone fracture [41]. The weight bearing reduction can be supported by analgesic or anti-inflammatory medication and physical therapy [11]. However, this may be very long lasting or even only delay the collapse of the femoral head. It has been shown that non weight bearing has a clinical success rate of 22.7%, whereas core decompression has a success rate of about 53% [3]. However, the outcome can be improved by the avoidance of risk factors, as discussed before. A lifestyle modification can also help to save the hip joint. This means a reduction of alcohol consumption and a stop of cigarette smoking, as well as a moderate physical training without shock load to the affected hip [8].

#### 1.7.1.1 Drugs

There are several medicaments in use for treatment of osteonecrosis. The most common is the stable prostacyclin analogue Iloprost. It is approved for therapy of critical ischemia secondary to peripheral arteriosclerosis, diabetic angiopathy or pulmonary hypertension [5] [11] [59]. It causes arterial and venous dilatation, reduces capillary permeability and reduces platelet aggregation. Besides the rheological effects on the terminal vascular bed, it has also the ability to reduce the concentration of oxygen radicals and leukotriens [58]. These effects improve microcirculation and so diminish the edema and thereby intraosseous pressure [12]. Administration of Iloprost is only helpful in very early stages, like bone marrow edema and ARCO I or II stages [23] [60]. When administered in these stages, it leads to a fast improvement of clinical symptoms and a significant pain reduction [61] [12]. The drug is given intravenously for five days, with a patient adapted increasing dosage [59]. However, there are several side effects of Iloprost. During infusion it may come to headache, nausea, flush or cardiac effects, like arrhythmia. A therapy with Iloprost is contraindicated during pregnancy, for patients with warfarin or heparin anticoagulation and for patients with peptic ulcers or with cardiological illness [58] [5] [62]. To improve success rate it is also possible to combine the operative core decompression with an Iloprost infusion. Both treatments alone show similar success rates, in combination there are less non responders and a higher success rate [11].

Other medicaments used for therapy of osteonecrosis are statins, which are mainly used in steroid induced ONFH or bisphosphonates, like Alendronate [59] [63]. Bisphosphonates have an antireabsorptive effect, by inhibiting osteoclast activity. Thus it leads to an increased bone density and may prevent subchondral collapse, in order to avoid surgical intervention [64]. Several studies showed that the short term results for Alendronate are mainly in ARCO I or II stages with small lesions quite promising. Pain as well as functionality improved significantly during a therapy with 10 mg Alendronate per day in combination with calcium and vitamin D [64]. In the long term results it could be seen that bisphosphonates given in pre-collapse stages can delay bone collapse up to 4.2 years [23] [59]. Nevertheless, there are some serious side effects, like mucosal irritation of the upper gastro-intestinal-system, osteonecrosis of the jaw bone or atypical femur fractures, which have to be taken into consideration [64].

#### 1.7.1.2 Other conservative measures

There exist some other, less popular nonoperative treatment ideas, like hyperbaric oxygen treatment (HBO) or extracorporeal shockwaves [10]. The hyperbaric oxygen is meant to reverse ischemia, by increasing the oxygen concentration in the tissue [59]. Although there is a pain reduction in the beginning, it has been shown that it cannot prevent subchondral collapse [23].

Extracorporeal shockwave therapy (ESWT) is a controversial discussed treatment option for early ARCO stages or in combination with other joint preserving therapies. It is meant to support neovascularization and regenerative, anti-inflammatory processes [65]. According to current data, ESWT is not able to delay the collapse of the femoral head [23].

### 1.7.2 Operative therapy

In the following tables 4 and 5 and in figure 3 there is given a short chronological overview of the literature about operative treatment of osteonecrosis of the femoral head.

| Year | Author | Journal | Title |
|---|---|---|---|
| 1955 | Koo et al. | Journal of Bone and Joint Surgery | Preventing collapse in early osteonecrosis of the femoral head- A randomised clinical trial of core decompression |
| 1985 | Ficat et al. | Journal of Bone and Joint Surgery | Idiopathic Bone Necrosis of the Femoral Head |
| 1994 | Adrian et al. | Journal of Bone and Joint Surgery | Long term results of core decompression for ischemic osteonecrosis of the femoral head |
| 2005 | Aigner et al. | Wiener Klinische Wochenschrift | Bone marrow edema syndrome of the femoral head: Treatment with the prostacyclin analogue iloprost An MRI-controlled study |
| 2006 | Mont et al. | Journal of Bone and Joint Surgery | Nontraumatic osteonecrosis of the femoral head: Ten years later |
| 2010 | Lee et al. | Chang Gung Medical Journal | Non-traumatic Osteonecrosis of the Femoral Head – From Clinical to Bench |
| 2014 | Li et al. | International Journal of Clinical and Experimental Pathology | Comparison of bone marrow mesenchymal stem cells and core decompression in treatment of osteonecrosis of the femoral head: a meta-analysis |

**Table 4: Literature Core decompression**

| Year | Author | Journal | Title |
| --- | --- | --- | --- |
| 2001 | Steinberg et al. | Clinical Orthopaedics and Related Research | Core decompression with bone grafting for osteonecrosis of the femoral head |
| 2010 | Fang et al. | Chinese Journal of reparative and reconstructive Surgery | Treatment of osteonecrosis of femoral head by core decompression combining with autologous cortical sustaining bone and cancellous bone graft |
| 2013 | Kang et al. | Yonsei Medical Journal | Clinical results of auto-iliac cancellous bone grafts combined with implantation of autologous bone marrow cells for osteonecrosis of the femoral head: a minimum 5-year follow-up |
| 2015 | Shah et al. | Journal of Clinical Orthopaedics and Trauma | Analysis of outcome of avascular necrosis of femoral head treated by core decompression and bone grafting |

Table 5: Literature Cancellous Bone Grafting


Figure 3: Literature operative therapies

#### 1.7.2.1 Core decompression

Core decompression is the most common operative hip preserving therapy at the time [57] [66] [58]. The primary aim of this intervention is a reduction of intraosseous pressure, which is meant to be the main pathological factor of osteonecrosis. With a decreased intramedullary pressure, there is a chance for normal blood circulation and so even revascularization is possible. This may lead, at least in theory, to bone remodeling and restitution of the necrosis [11] [5] [67]. The reduced hypertension in the bone explains why most patients have a significant pain reduction after the operation [68] [69] [70]. Nevertheless, there are many different success rates described in literature. When Ficat first brought up this method, he found an overall clinical success rate of 89.5%. He also showed that outcome is very much dependent on the stage of the necrosis, as he came up with success rates of 93.9% for stage I and 82.5% for stage II. The radiographic results, however, were not that positive. Here could have been shown an improvement rate of 78.9% [9]. Later studies show a wide range of success rates. It is settled somewhere between 63.5% and 84%, but only in early stages of the disease [66] [13] [3] [10]. In most cases the clinical symptoms of patients can be improved, although radiographic progression of the necrosis is visible. Only in very early stages the disease is reversible. But the earlier core decompression is performed, the better are the long term results for the patients. Size and location of the affected area are also important risk factors for the outcome of core decompression [66] [13] [67].

The procedure of core decompression is quite easy. The patient is in general or spinal anesthesia and the location of the necrotic area is detected with C-arm imaging. Then surgery is performed by a lateral approach. A guide pin is drilled from the proximal lateral femur, about 4 cm below the trochanteric ridge, into the lesion. When aiming is confirmed by C-arm image, a core reamer is drilled over the guide pin and creates a 10 mm bone channel. After that the necrotic bone can be removed [57] [13]. This way of performing the core decompression brings the risk of subsequent collapse of the femoral head, as well as an increased danger of proximal femur fracture, in case of weakening the cortical wall of the femoral neck. A complication rate of about 4% to 10% has been described.

Thus there is also the possibility to perform a multiple drilling with small pins in a fan-shaped way. There seems to be no significant difference in success rates, but the multiple drilling shows less complications, like subtrochanteric fractures or hip joint penetration

[67] [8]. However, it is a disadvantage that there can´t be taken histological samples and it is not possible to perform cancellous bone grafting.

As it is crucial to penetrate the necrotic area, there is also the possibility to perform core decompression with a navigation system. It showed that the precision of the drilling could be improved and the radiation time was shorter than in conventional procedure [71] [72].

For the performance there has to be a virtual connection of the fluoroscopic images and the position of the surgical instruments. This makes it necessary to attach markers to the surgical instruments, the patient and the C-arm. Therefore, a reference array with passive reflecting marker spheres is attached to the surface of the patient and the instruments. Visualization of the necrotic area has to be done by the C-arm fluoroscope, which is connected to the navigation system. After that no further intraoperative images are needed. A standard drill is equipped with a marker-clamp and measured with a special calibration tool in order to inform the navigation system about the length, diameter and position of the tip of the instrument. After the surgical instrument is visualized on the touch-screen monitor, the drill is placed into the bone by continuous online control of the navigation system. Virtual connection of the position of all the reference markers enables the orientation of the drilling guide in two fluoroscopic planes simultaneously. This may lead to a significant reduction in the distance to the target when compared with conventional core decompression (0.4 mm in the navigation group versus 0.88 mm in the conventional group). Another benefit can be seen in the reduced radiation time. There is an obvious difference between navigated core decompression and the traditional procedure. It has been shown that the radiation exposition can be reduced for the patients and the staff from 3.1 seconds to less than one second [71] [72].

Postoperatively partial weight-bearing is recommended for six to eight weeks. During the first period of full weight-bearing, high impact activities should be avoided for about one year. Physiotherapy should be performed to strengthen the muscles and to regain range of motion [14].

Core decompression can also be combined with autologous bone grafting. There exist different kinds of grafts. The first possibility is to transfer vascularized or nonvascularized bone grafts, like a part of the fibula or the tibia. The main goal of these transplants is to strengthen the femoral head, in order to avoid a collapse or a fracture [73] [57] [17]. It is also possible to transfer cancellous bone from the iliac crest, greater trochanter or proximal femur into the bone channel. It is suggested that the cancellous bone contains osteoprogenitor cells, which may improve healing and structural recovery of the necrotic lesion [74] [8]. A comparable method is the implantation of bone marrow mesenchymal stem cells. These cells have been suggested to promote osteogenesis and angiogenesis, which leads to a reduction of symptoms in the short term, but also to a shortening of the disease and a partial recovery of the necrotic area [66].

Although core decompression has been performed for about three decades, its effect on the progression of osteonecrosis is still not clear. There are some hints that combined methods, like bone grafts and mesenchymal stem cell implantation might bring better results than core decompression alone. It has to be considered that core decompression is helpful particularly in early stages [57] [66] [3] [75].

#### 1.7.2.2 Proximal femoral osteotomy

Whereas core decompression can only be performed in early stages and before collapse of the hip joint occurs, osteotomy can also be helpful in early post-collapse stages [8] [2]. The main goal of osteotomy is to transfer the necrotic bone area out of the major weight bearing area. This leads to a relief of the necrotic or collapsed lesion and thus to a reduction of pain and a delay of progress. Another positive side effect of the operation might be a reduction of intraosseous venous pressure and thereby an improved vascularity as described before [67] [17]. There are mainly two types of osteotomy: the trans-trochanteric rotational osteotomy and the intertrochanteric varus or valgus osteotomy [8] [10]. The trans-trochanteric rotational osteotomy allows a large degree of translation of the necrotic area; however, the intertrochanteric osteotomies are less technically demanding [2]. Criteria for the performance of an osteotomy are an age under 45, an early postcollapse or late precollapse stage, no joint space narrowing or acetabular involvement, a small to medium lesion and no history of high dose steroid intake [2]. Success rates vary a lot in literature. It might be somewhere between 60% to 93% long term hip survival rate [67] [2]. Although the results seem to be quite good, osteotomies are seldom performed and not well accepted by patients. This may derive from its great invasivity, its technical complexity or the potential risk of morbidity. Common problems are a nonunion of the bones and there are reports that a total hip replacement after failed osteotomy is often connected with difficulties or complications [8] [2] [67]. The ongoing improvement of arthroscopy may help surgeons to visualize and quantify cartilage damage and so lead to better long term results [8].

#### 1.7.2.3 Total hip arthroplasty

When the disease progresses, joint preventing therapy is almost impossible. In these cases total hip arthroplasty may be the only solution left. It is an effective and viable option for patients with an extensive postcollapse lesion, with secondary osteoarthritis or acetabular involvement [67] [2]. Total hip replacement leads to significant pain reduction and good functional outcome [2]. However, there are some concerns for this treatment. As mostly younger patients are affected, there is a high possibility for revision arthroplasty. There are also some reports about polyethylene wear and osteolysis leading to aseptic loosening of total hip replacement after ONFH. This was mentioned in about 8% to 31% of cases after ONFH. In recent times, survivorship of implants increased due to new materials, like ceramic bearing or porous materials [67]. Even several risk factors may affect the duration of total hip replacement after osteonecrosis, like steroid intake, alcohol abuse, systemic lupus erythematodes or organ transplantation [2] [1]. The decision for cemented or cementless total hip arthroplasty has to be done by clinical issues. The cemented implant may have a higher loosening rate, whereas the cementless implant showed periprosthetic osteolysis [1]. There are reports that patients with ONFH prior to total hip replacement have a decreased bone mineral density in comparison to patients with THR due to degenerative processes. This effect was visible in the acetabular region as well as around the femoral system. This may be an explanation for high loosening rates among patients with total hip replacement after AVN [76] [77].

An alternative to total hip replacement might be limited femoral resurfacing arthroplasty. It is mostly an option for large lesions with late stages, but without acetabular involvement. The benefit is that femoral head and neck bone stock are preserved, which means that revision to total hip arthroplasty is not complicated thereby [19] [2]. In the meantime it is seldom performed because studies showed high failure rates up to 31% [67].

# 2. Question

As there are many different therapy concepts and no common consent about the effectiveness of each, it is of great importance for the mostly young patients to get facts about the clinical outcome of the different treatments. It is also inevitable to test and to introduce new methods of therapy concepts and of quality management.

In the light of the above this study is built up of three different questions.

The first part is a retrospective trial to show the **effectiveness of common head preserving therapy concepts** of ONFH. The goal is to judge the different treatments according to patients' subjective feelings and to the clinical outcome. For that patients were split up according to the therapy they had. The first group included only patients treated with core decompression. Patients in the second group were treated with core decompression in combination with autologous cancellous bone grafting. In order to get comparable results, only patients with an ARCO II avascular necrosis of the femur head were taken into account. Each therapy group was operated by one surgeon. Surgeon 1 always performed the core decompression, surgeon 2 made the cancellous bone graftings. Both collectives were matched according to sex and age.

The second part deals with new technical methods to **measure the precision of core decompression**. By virtual three dimensional reconstruction and measurement of the necrosis and the drill hole it shall be given an impression to coming possibilities in modern medicine. It has to be discussed whether conventional core decompression by C-arm imaging is really exact enough to get into the center or at least, into the area of the necrotic bone. Furthermore it shall be assessed if there is a difference in precision between the drilling with the small pins and the trephine.

The third part deals with **bone marrow perfusion measuring**. This is a quite new topic, as there exists only very little literature about bone marrow perfusion measuring. There are some reports that there is a connection between reduced bone mineral density (BMD) and an impaired bone marrow perfusion in patients with osteoporosis. Another field of application may be the differentiation between benign and malign changes within the bone marrow [78] [79]. As this technology is not established in clinical routine so far, we tried to make a descriptive work about a possible application in femoral head necrosis as a basis for future analysis.

# 3. Material and Methods

## 3.1 Patients

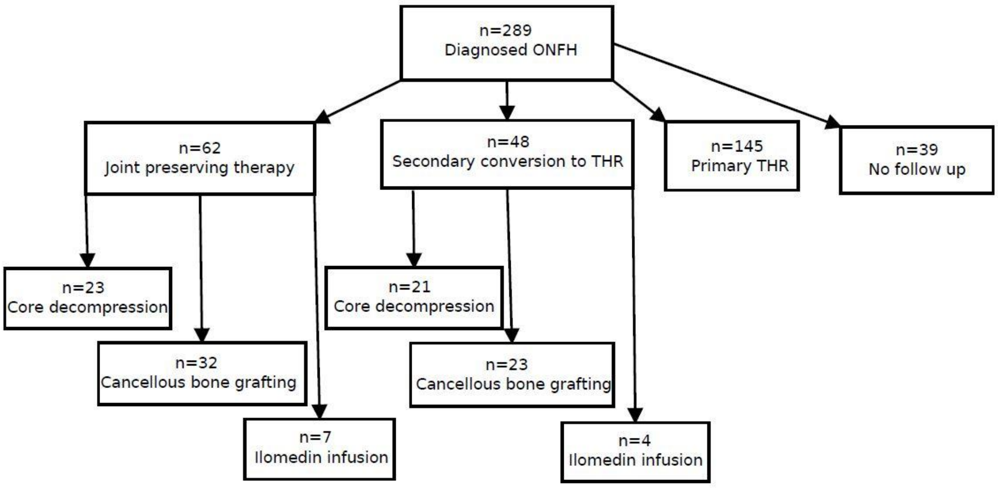


**Figure 4: Overall patient collective in the period from 2006 to 2012**

In figure 4 above the overall patient collective is shown. There were all patients included, who had a treatment for a diagnosed osteonecrosis of the femoral head at the Department of Orthopedic Surgery, University of Regensburg, during the time from 2006 to 2012. In this time there were 289 hips with a diagnosed avascular necrosis. 145 of these hips were primarily provided with a THR, because the stage was already progressed or it was the patients` wish. 110 affected hips were tried to treat with joint preserving therapies like core decompression, autologous cancellous bone grafting, Ilomedin infusions or combination of core decompression or cancellous bone grafting with Ilomedin infusion. 48 femoral heads aggravated despite of the therapy, so they had to undergo total hip replacement. The other 62 femoral heads showed no aggravation which would have made a prosthetic treatment necessary. This group represents the main patient collective, observed in this survey.

For the survey only the patients who did not need THR were taken into account. So there were 57 patients with 62 treated hips, who met our inclusion criteria. These 44 men and 13 women were contacted written and by phone call. There was no answer from 20 persons. Three patients did not want to come to the hospital for examination, because their hip was good so far. Two patients denied participation without a statement, one denied due to current problems with his treated hip. In one case the patient had to undergo THR in the mean time and one patient had passed away. A total of 28 patients with 32 treated hips had to be excluded (overview see figure 5).

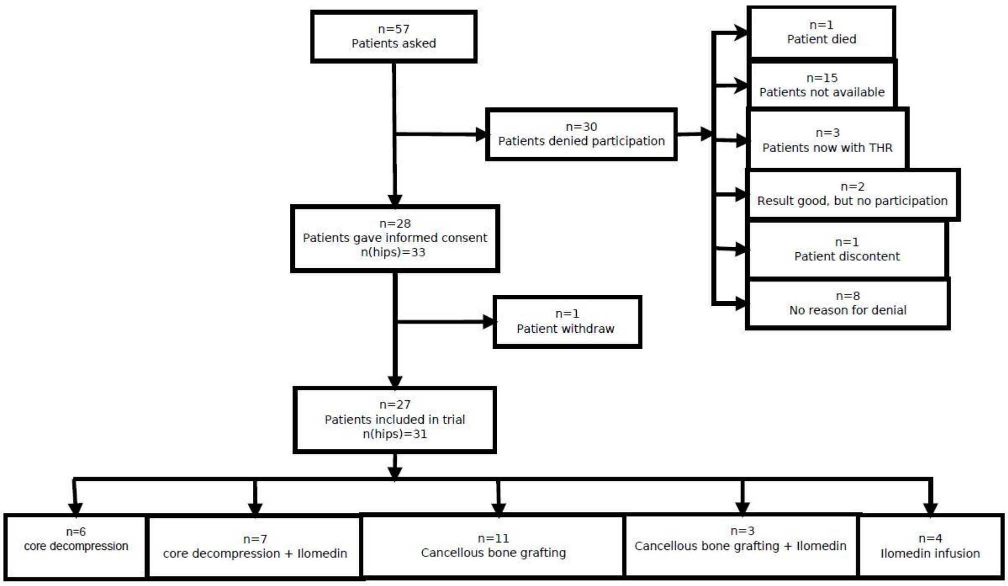


**Figure 5:** Consort Diagram**: Joint preserving therapy**

In general, 29 patients with 31 treated hips were left for this study (see table 6 below). Nine (31.03%) female and 20 (68.97%) male patients, with a mean age of 43 years (SD 10.15, range 22-61) when being treated could be included in this study.

There was 14 times the left hip affected and 17 times the right one. Bilateral involvement was prevalent in two male patients.

Body mass index (BMI) ranged between 21.2 kg/m$^2$ to 33.8 kg/m$^2$ with a mean BMI of 27.09 kg/m$^2$ and a SD of 2.79 kg/m$^2$.

Patients were categorized according to the ARCO classification [80]. Stadium I was found five times, stadium II 23 times and stadium III three times.

No systematic disease, like sickle cell anemia, Gaucher's disease, Caisson disease or autoimmune diseases (systemic lupus erythematosus, Sjögren's syndrome or scleroderma) were reported in this group. One patient had a hip injury. One patient had a hyperuricemia and one patient a hyperlipidemia. Five patients reported subjective alcohol abuse and five patients reported subjective nicotine abuse. Eight patients had a history of corticosteroid intake.

Four patients were treated with an Ilomedin infusion therapy and 14 hips with core decompression (CD) with K-wire in a fan shaped fashion. Of these 14 joints, seven cases were additionally treated with an Ilomedin infusion. On 14 femoral heads core decompression (CD) with autologous cancellous bone grafting of the iliac crest was performed. Three of them had an additional Ilomedin infusion.

| | Mono therapy | | Double therapy | | Triple therapy |
|---|---|---|---|---|---|
| Therapy-Group | 1 | 2 | 3 | 4 | 5 |
| | CD | Ilo | CD + CBG | CD + Ilo | CD + CBG + Ilo |
| male (n) / female (n) | 4/2 | 4/0 | 8/3 | 5/2 | 1/2 |
| mean age(years); min/max; SD | 44.5; 30/54; 9.4 | 52.0; 41/57; 6.6 | 40.9; 22/54; 10.0 | 40.4; 28/54; 8.7 | 45.3; 30/61; 12.7 |
| mean BMI ($kg/m^2$) min/max; SD | 27.7; 27.5/29.3; 3.7 | 26.8; 25.3/27.7; 4.4 | 27.3; 24.3/33.8; 1.6 | 26.9; 21.2/33.5; 2.4 | 25.8; 25.6/26.3; 1.4 |
| ARCO(n): I II III | 1 5 0 | 3 1 0 | 0 10 1 | 1 6 0 | 0 1 2 |

**Table 6: Baseline table of treatment groups with number (n) of patient depending on ARCO stage (CD core decompression; CBG: cancellous bone grafting; Ilo: Ilomedin infusion)**

The mean disease free survival was 4.93 years (59.1 months), with a range from 26.3 to 92.9 months.

All patients gave written informed consent to the study.

As a comparison group we observed the patients who had to undergo THR after a joint preserving therapy attempt. There were 46 patients with 48 treated hips. The mean age of these subjects was 46 years, with 32 male and 14 female persons. In general there was a mean period of 10.6 months, with a range from 1.3 to 67.6 months, between the first joint preserving trial and the final prosthetic treatment. Table 7 below shows the baseline characteristics of this group with differentiation according to the treatment.

| **Group** | **CD** | **CD + CBG** | **Ilo** |
|---|---|---|---|
| **male (n) / female (n)** | 15/6 | 17/6 | 2/2 |
| **mean age (years); min/max; SD** | 50.4; 30/72; 11.0 | 42.4; 29/73; 10.9 | 47.5; 22/61; 15.1 |
| **ARCO (n):** | | | |
| **I** | 2 | 0 | 0 |
| **II** | 11 | 14 | 2 |
| **III** | 7 | 9 | 2 |
| **IV** | 1 | 0 | 0 |
| **Time between first joint preserving therapy and THR (months); min/max; SD** | 9.5; 1.3/26.8; 7.0 | 11.3; 3.0/67.6; 12.9 | 11.9; 4.9/20.4; 5.6 |

**Table 7: Baseline characteristics with number (n) of patients with conversion to THR (CD: core decompression; CBG: cancellous bone grafting; Ilo: Ilomedin infusion)**

The patients with a history of conversion from joint preserving therapy to THR were not contacted or clinically examined.

## 3.2 Groups

All patients of the examined collective were split up into groups according to the question of the survey.

### 3.2.1 Comparison between core decompression and cancellous bone grafting

For the first part of the study 22 patients met the participation criteria (Table 8). There were three inclusion criteria, which led to a rather small number of patients. First of all only patients with a diagnosed osteonecrosis in ARCO stage II before treatment were taken into account. They were set up into two different groups, according to the previous therapy. Half of the patients had a history of core decompression, the others were treated with additional cancellous bone grafting. The second criterion was that both populations had been operated by the same surgeon each. Surgeon 1 performed the core decompressions of group 1. Surgeon 2 did the cancellous bone graftings after core decompression in group 2. As a third condition the cases were matched according to sex and age in both groups. By this eleven patients in each group were left. In general there were 14 male and eight female persons. The mean age was 41.3 years in group 1, with a range from 28 to 54, and 42.0 years in group 2 with range from 22 to 54. In group 1 the mean BMI was 26.4 kg/m², with a range from 21.2 to 29.3 kg/m² and a standard deviation of 3.2 kg/m². The mean BMI in group 2 was 27.4 kg/m², with a range from 24.3 to 33.8 kg/m² and a standard deviation of 2.7 kg/m². The mean follow up time of patients with core decompression was about 4.0 years (48.0 months), with a range from 26.3 to 68.5 months. The mean follow up time in patients with cancellous bone grafting after CD was about 5.2 years (69.2 months), with a range from 38.0 to 92.9 months.

| Group | Group 1: CD | Group 2: CD + CBG |
|---|---|---|
| **male(n) / female(n)** | 7/4 | 7/4 |
| **mean age (years); min/max; SD** | 42.3;<br>28/54; 8.9 | 41.9;<br>22/61; 10.8 |
| **mean BMI** (kg/m$^2$); min/max; SD | 27.1;<br>21.2/33.5; 3.5 | 27.2;<br>24.3/33.8; 2.4 |
| **ARCO stage II (n)** | 11 | 11 |

**Table 8: Core decompression vs. cancellous bone grafting (CD: core decompression; CBG: cancellous bone grafting; Ilo: Ilomedin infusion)**

The patients in whom joint preserving therapy had failed were spilt according to the respective therapy group. In the core decompression group there were 21 subjects, 23 had a history of cancellous bone grafting and four persons had an Ilomedin infusion therapy (see table 7 above).

### 3.2.2 Precision measurement of core decompression

In the second population were only patients treated with core decompression. 15 (79%) male and four female (21%) patients, treated between the years 2007 and 2013, were included in this analysis. Bilateral femoral head necrosis was only prevalent in three men, leading to 22 hips available for this study. The overall mean age of the patient collective was 41.2 years with a standard deviation (SD) of 9.9 years.

Body Mass index (BMI) ranged between 21.2 kg/m$^2$ and 33.8 kg/m$^2$ with a mean BMI of 27.1 kg/m$^2$ and a SD of 3.3 kg/m$^2$.

In unilateral cases about 60% of the cases the right hip was affected, in 40% of the cases the left hip was affected.

Patients were divided into two groups. Group A only contained patients with core decompression alone. Group B represents patients with cancellous bone grafting after core decompression as therapy (see Table 9). In group A there are ten cases; in group B there are twelve hips after cancellous bone grafting. There was no discrimination between ARCO stages.

| Group | A: CD | B: CD + CBG |
|---|---|---|
| **male (n) / female (n)** | 7/3 | 11/1 |
| **mean age (years);<br>min/max;<br>SD** | 43.1;<br>28/54;<br>9.3 | 40.0;<br>22/54;<br>10.1 |
| **mean BMI (kg/m²);<br>min/max;<br>SD** | 26.7;<br>21.2/33.5;<br>3.9 | 27.4;<br>24.3/33.8;<br>10.1 |
| **ARCO (n):<br>I<br>II<br>III** | <br>2<br>8<br>0 | <br>0<br>9<br>3 |

**Table 9: Patients for three dimensional precision measuring (CD: core decompression; CBG: cancellous bone grafting)**

### 3.2.3 Quantitative measurement of femoral head perfusion

The third group only contains patients who had a special contrast agent MRI. This was not possible to perform in every case. One patient already had a contrast agent, so he could not be given another dosage. One patient could not be given contrast agent due to allergy. One patient had already had a MRI so she did not want to perform another one. Of one patient there could not be done MR imaging, due to his claustrophobia. One patient denied informed consent to MRI. In general, five patients had to be excluded. There remained 24 patients with 26 treated hips in this survey. There was no limitation according to ARCO stage or therapy regimen. There were 18 male and eight female patients included. Three hips were classified as ARCO I, 20 hips as ARCO II and 3 hips were ARCO III. The mean age in this group was 41.1 years. Eleven patients were treated with core decompression. Six of them had gotten additional Ilomedin infusion. Cancellous bone grafting was performed at twelve hips, one with supplementary Ilomedin infusion. Three patients were treated with Ilomedin infusion only. The exact distribution of therapy and ARCO stage is shown in table 10 below.

| | Mono therapy | | Double therapy | | Triple therapy |
|---|---|---|---|---|---|
| **Therapy-Group** | **1** | **2** | **3** | **4** | **5** |
| | **CD** | **Ilo** | **CD + CBG** | **CD + Ilo** | **CD + CBG + Ilo** |
| **male / female** | 3/2 | 0/3 | 10/1 | 4/2 | 1/0 |
| **mean age (years); min/max; SD** | 42.8; 30/43; 8.6 | 51.7; 41/57; 7.5 | 40.9; 22/54; 10.0 | 40.0; 28/54; 9.3 | 30.0 |
| **mean BMI (kg/m²); min/max; SD** | 28.4; 27.5/29.3; 0.7 | 26.6; 25.3/27.7; 1.0 | 27.5; 24.3/33.8; 2.6 | 25.7; 21.2/33.5; 4.7 | 26.3 |
| **ARCO (n)** | | | | | |
| **I** | 0 | 2 | 0 | 1 | 0 |
| **II** | 5 | 1 | 9 | 5 | 0 |
| **III** | 0 | 0 | 2 | 0 | 1 |

**Table 10: Patients for perfusion measuring (CD core decompression; CBG: cancellous bone grafting; Ilo: Ilomidin infusion)**

## 3.3 Clinical protocol and scores

In the following chapters the different protocols of three subgroups are explained.

### 3.3.1 Clinical comparison between core decompression and cancellous bone grafting

All patients with a successful joint preserving therapy were examined according to the same study protocol: physical examination of the hip, including range of motion (ROM), pain-level or any contractions of the hip joint. The ROM was calculated as a sum score of hip flexion, adduction, abduction, internal and external rotation. This refers to the range of motion in the Harris Hip Score, with 300° to 210° being an excellent result, 209° to 160° a good result, 159° to 100° a moderate result and <100° a poor result [81]. Followed by clinical standard procedure with radiological imaging, including plain radiographs in anterior-posterior projection and as a second plane in Lauenstein projection. Thereafter, a MRI was performed. At last patients answered several scores, including the Harris Hip Score (HHS), Hip Disability and Osteoarthritis Outcome Score (HOOS), EuroQol 5D (EQ-5D), Short Form 36 Questionnaire (SF-36) and pain intensity during rest and physical strain with use of the Visual Analogue Scale 10 mm (VAS).

The evaluation of the radiological images was based on the ARCO classification. Therefore the plain radiographs and the MRI images were assessed. So all examined hips could be given a current staging.

The evaluation of the HHS was done on the online platform www.orthopaedicscores.com. Therefore patients´ answers were transferred anonymously to the website and the score was calculated.

The appraisal of HOOS was also performed on www.orthopaedicscores.com. Patients answers were again transferred anonymously and the program reckoned the final score.

EQ-5D analysis was performed according to Hinz A et al. [82], using the recommended sum-model. This leads to a possible score between 0-100, with a high sum score representing a high life quality. The test assesses the subjective health status according to five different levels: mobility, the ability to look after oneself, activity of daily life, pain and fear.

SF-36 score was evaluated in every single dimension of the test, giving an overview about the general life quality.

### 3.3.2 Three dimensional measurement of drilling precision

Of all patients magnetic resonance imaging (MRI), using a Philips Ingenia 1.5 T magnetic resonance imaging system with a digital surface coil, of the pelvis and the hip was retrieved. The imaging was performed in supine position. MRI slices were saved in DICOM format with a slice thickness of three millimeters and 20 slices in each weighting.
3D reconstruction, segmentation and measurements were done using Simpleware Scan IP (Simpleware, Exeter, UK).
The method derives from the susceptibility artifacts in the MRI technology. This means that during the drilling micro metal particles of the drill are abraded. Those particles can be detected postoperatively by MRI.
The drill hole and the necrosis areal as the regions of interest (ROI) were marked using the provided manual segmentation tools (figure 6). In order to allow 3D reconstruction the ROI has to be manually segmented in all three dimensions. Both, necrosis origin and drill holes were reconstructed in this manner.

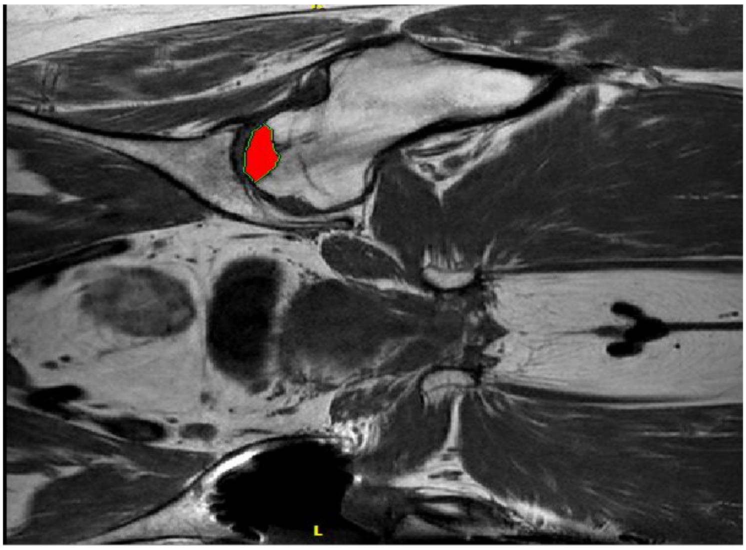


**Figure 6: Segmentation of the necrotic area**

**Figure 7: Necrotic area without segmentation**

In figure 6 the necrotic area is colored in red. It has been marked as a ROI with the manual segmentation tool. Figure 7 represents the necrosis before the segmentation process. This marking of the defect zone has to be repeated in every slice of the MRI in which the necrosis is visible. The same has to be done with the drill channel. In figure 6 a short part of the drill channel can be seen underneath the necrosis. In this case a core decompression with a small pin had been performed.

By applying an 'extended marching cube algorithm'3D reconstruction was ultimately achieved, from which the measurements were taken. For this the maximum elongation of the drill hole and the necrosis areal was measured in millimeters in all three spatial planes (xyz) as a vector. Of these two vectors (drill hole and necrosis areal) the center point was measured. The deviation of the center point of the drill hole to the center point of the necrosis areal is a measure of how accurate or precise a drill channel can be placed into the femoral head in order to meet the necrotic area. An alignment of both center points is desired. If the drill hole was achieved in a fan-shaped fashion, the center point of all three tips of the drill holes was determined (as described above) and the deviation from the center point of the necrosis was measured. The schematic drawing below (figure 8) shows how the distance between the center point of the necrosis and the center point of the drill hole is measured.

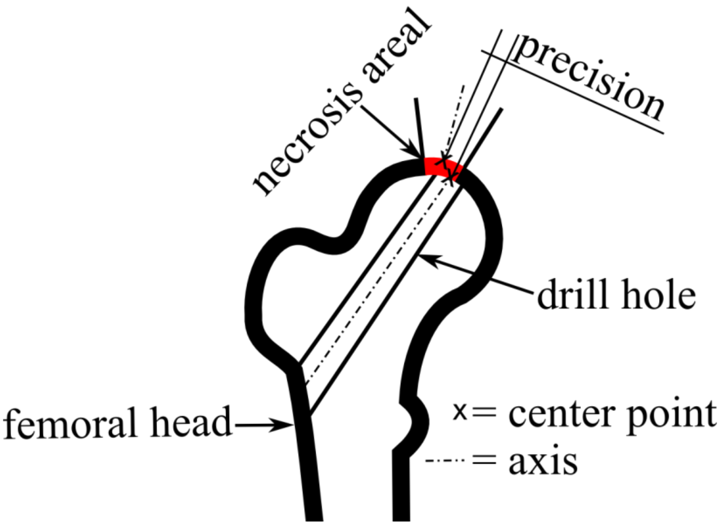


Figure 8: A schematic drawing of the definition of precision

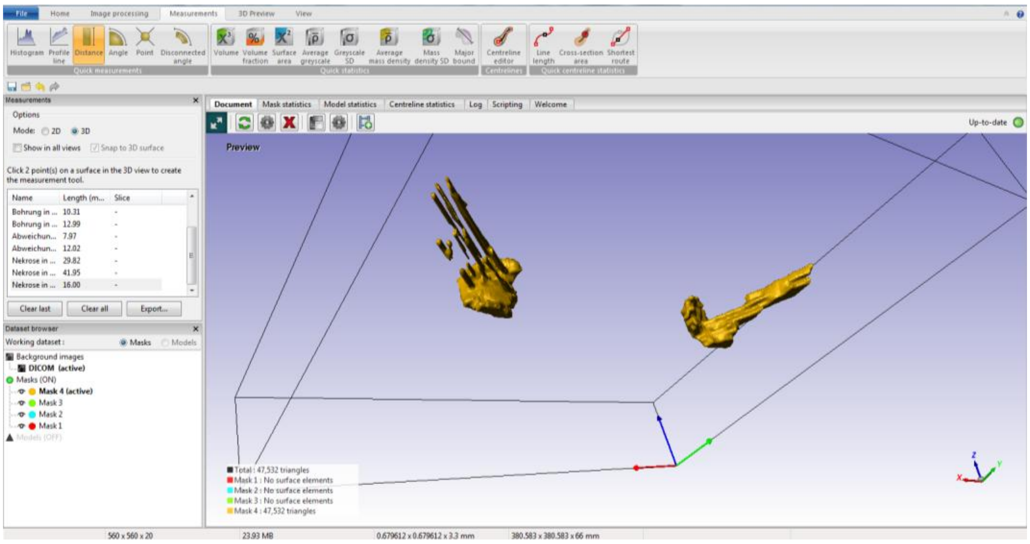

**Figure 9: Program surface with three dimensional reconstructions**

In figure 9 the reconstructed formation is shown in the three dimensional coordinate system, before measurements are performed. It shows the surface and the tools of the program.

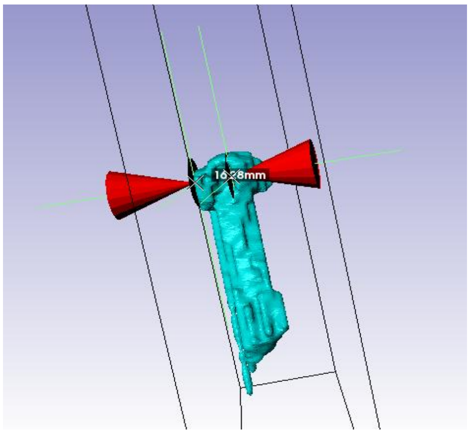


**Figure 10: Measurement of the center point of the necrosis**

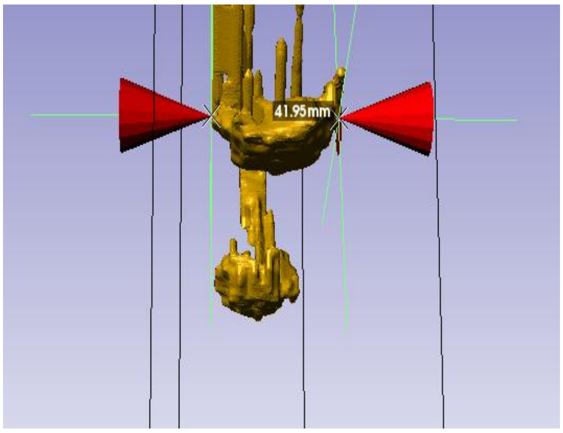


**Figure 11: Measurement of the necrotic area in the x-axis**

Figure 11 shows the measurement of one necrotic area in the x-axis. This procedure had to be performed in every axis and the center point had to be found for each (figure 10). The same working steps had been performed for the drill channels.

### 3.3.3 Semiquantitative measurement of the hip perfusion

The measuring of the hip perfusion was done by clinical standard with a contrast-agent improved T1 weighted sequence (DIXON) in the MRI, using a Philips Ingenia 1.5 T MR. Imaging was performed in supine position with a digital surface coil. Dynamic images were obtained using a short T 1 weighted gradient echo sequence (mDIXON_W_dyn_tra; TE: 1.8/ 3.9 ms; TR: 5.6 ms; flip angle 15°). The contrast agent was Dotarem® (Gadoleic-acid) Guerbet-company, with a concentration of 0.2 ml/kg/BW. The application was done via high-pressure-injector by Med-Tron-company, with a flow rate of 2 ml/sec. The injection was followed by a 20 ml NaCl flush, with a flow rate of 2 ml/sec. Dynamic MR imaging started with a maximum delay of 17 seconds after contrast agent injection.

The examination is composed of four series of axial slices. The first series is performed native, without contrast agent. Thereafter follow three sequences at different times after the application of the contrast agent.

At first the reference slice has to be determined, hereby that slice has to be chosen in which the femoral head shows the biggest diameter (figure 12). Thereafter follows the determination of the signal intensity by a so called ROI-measurement (region of interest). Here it is important, that the ROI´s circle occupies the femoral head sub-maximally. The cortical bone should not be occupied by the ROI (figure 13). So only the contrast signal intensity in the bone marrow is measured.

Every single one of the four performed measures has to be done with the same sized ROI at the identical slice. The first ROI is set in the native slice, so it works as a blank value.

The following three series are performed at defined times after the injection of the contrast agent. They are taken at different stages of distribution in the bone marrow (figure 14). In the figures 13 and 14 there are shown two measurements of the same patient at different times after the contrast agent injection. According to the distribution of the agent the signal intensity is not identical in both. It can be seen that the ROIs are always set in the identical place and the same slice (represented by the “table position”). In theory the relation of the signal increase in the ROI after the contrast agent has been administered shows the amount of perfusion in the femoral head and allows a comparison between different patients or may enable to draw conclusions about certain pathologies.

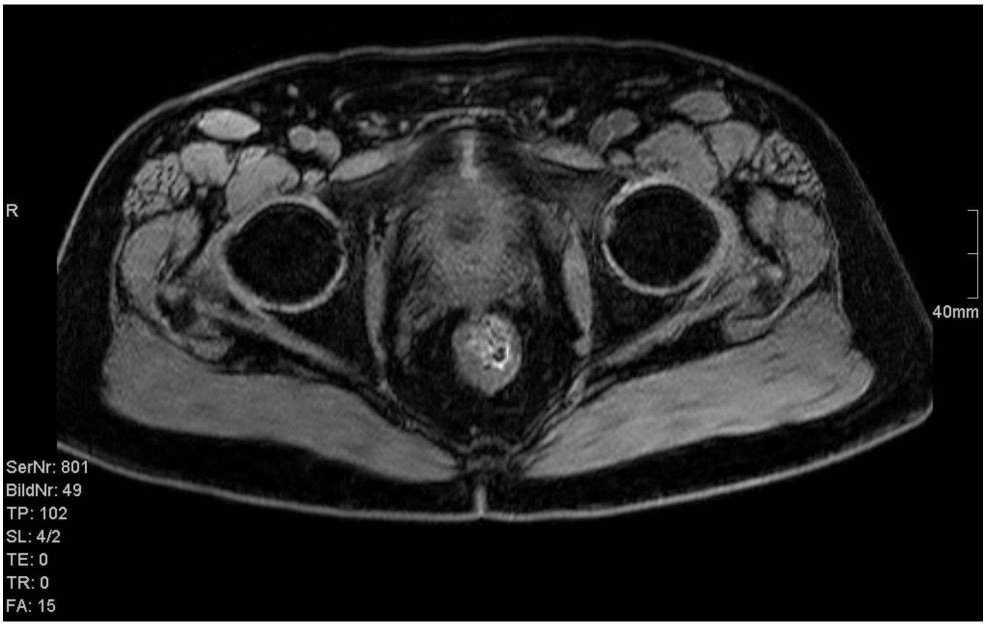


**Figure 12: Determination of the slice in which the femoral head shows the maximum diameter (TP: table position)**

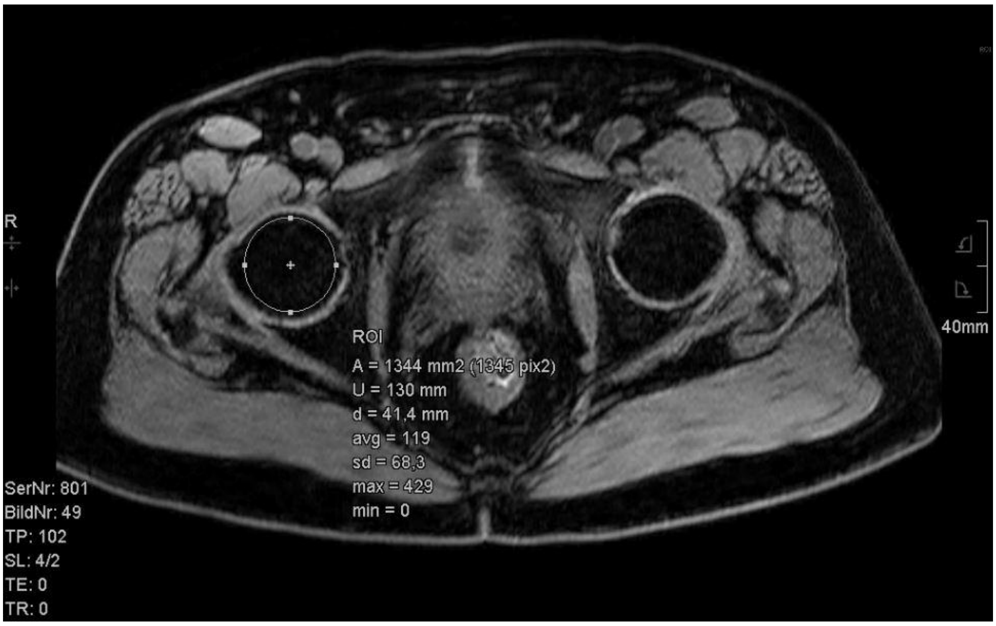


**Figure 13: Performance of ROI-measurement (A: area; U: perimeter; d: diameter; avg: average signal intensity; sd: standard deviation; max: maximum signal intensity; min: minimum signal intensity; TP: table position)**


**Figure 14: ROI-measurement in following distribution phase. (A: area; U: perimeter; d: diameter; avg: average signal intensity; sd: standard deviation; max: maximum signal intensity; min: minimum signal intensity; TP: table position)**

## 3.4 Statistics

Statistical analysis for the comparison between the two groups was carried out using the *t* test for the clinical test results and the earlier described scores. In these cases when normality testing failed and t-test could not be used, the Mann–Whitney Rank Sum Test was applied. All analyses were performed using SigmaPlot 11.0 (Systat Software Inc., Chicago, IL, USA). Statistical comparisons were made at a 0.05 level of significance.

# 4 Results

### 4.1.1 Clinical comparison of core decompression and cancellous bone grafting

With the performed check up examination we wanted to see if core decompression or cancellous bone grafting is superior to the other.

At first we wanted to know if patients suffered pain in their treated hips. For that they were asked to mark their pain level on a scale from 0 to 10, meaning from no pain at all to the worst even imaginable pain (according to the VAS). The patients were asked to do the marking one time for the pain level during rest and the second time during hard physical strain. A medium pain (VAS 5) during rest was given only by one patient in group 1 (core decompression). In group 2 (cancellous bone grafting) there were two patients with very mild pain (VAS 1) and one case with medium strong pain (VAS 5) during rest. For the pain level during strong physical strain patients with core decompression stated a medium pain level of 3.3 with a range from 0 to 8. The medium activity pain in the cancellous bone grafting group was 2.2 with a range from 0 to 7. There could be shown no significant difference between the two therapies (Figure 15).

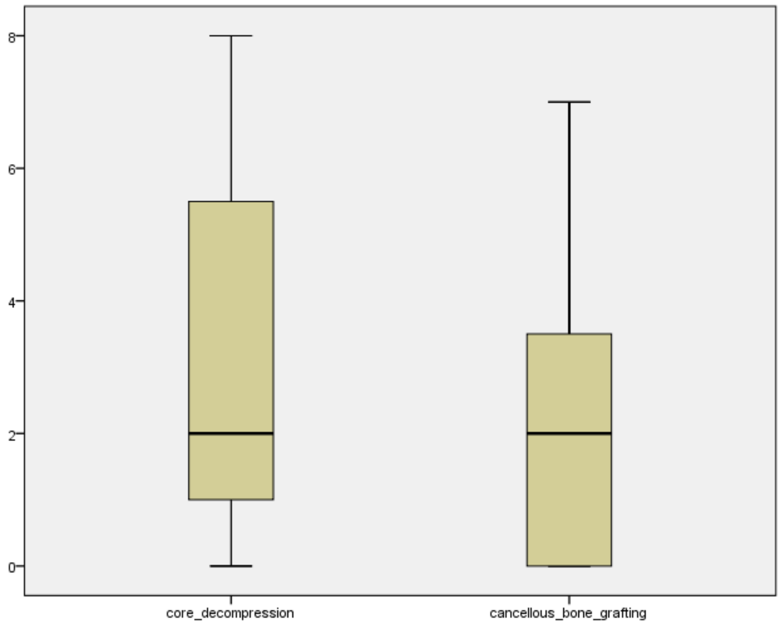


**Figure 15: Box plot VAS during physical strain**

In the clinical examination the range of motion of the treated hip was tested and documented in degrees. The test scores in every movement axis (flexion, adduction, abduction, internal and external rotation) were added up to a total Range of Motion score. In group 1 there was a mean range of motion of 224.5° with a range from 190° to 265°. The mean score in group 2 was at 232.9°, ranging from 140° to 280°. T test showed p=0.225 and therefore no significant difference between the two groups (figure 16).

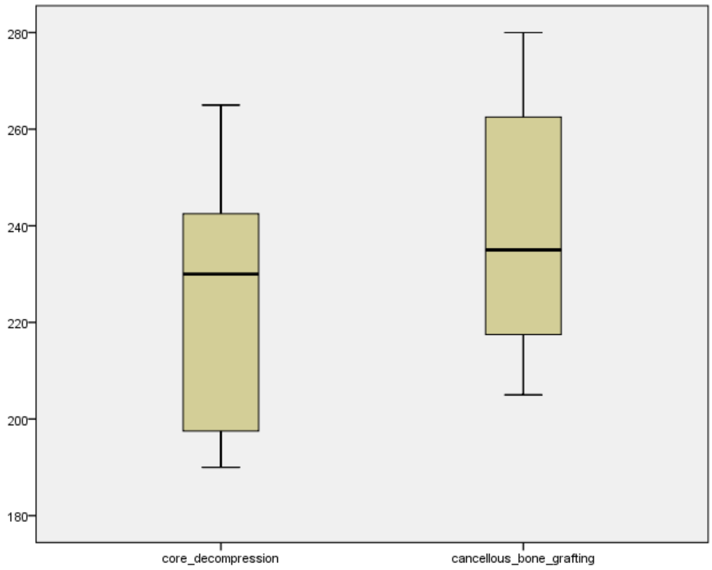


**Figure 16: Box plot range of motion**

All patients were asked to answer several questionnaires about their general well being and the state of the operated hip. The comparison of the two therapy groups revealed no statistical significant difference in any of the scores. In the hip specific "Harris Hip Score" and "Hip disability and Osteoarthritis Outcome Score" the bone grafting group showed slightly better results, however they were not statistically significant (see table 11 and figure 17 and 18). Patients with core decompression achieved better results in the SF 36 score, but again without any significance.

| Score | CD | CD + CBG |
|---|---|---|
| **Harris Hip Score**<br>mean value (range, p) | 87.7<br>(58-100, 0.362) | 93.2<br>(58-100, 0.362) |
| **HOOS**<br>mean value (range, p**)** | 75.6<br>(37.2-95, 0.470) | 81.2<br>(37.2-100, 0.470) |
| **EQ-5D**<br>mean value (range, p) | 79.1<br>(50-100, 0.788) | 80.9<br>(60-100, 0.788) |
| **SF 36 physical health**<br>mean value (range, p) | 46.6<br>(21.2-56.2, 0.599) | 42.3<br>(20.1-57.3, 0.599) |
| **SF 36 mental health**<br>mean value (range, p) | 53.2<br>(37.8-59.6, 1.000) | 49.8<br>(32.9-61.3, 1.000) |

**Table 11: Evaluation clinical scores (CD: core decompression; CBG: cancellous bone grafting)**

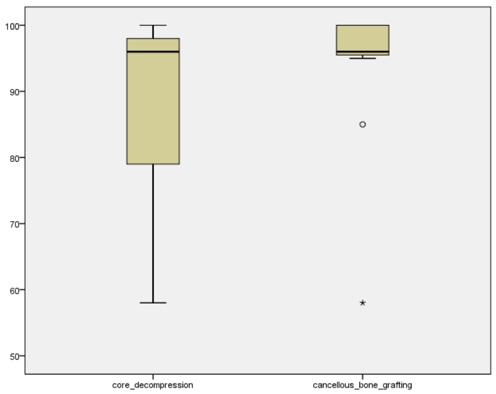


**Figure 17: Box plot Harris Hip Score**

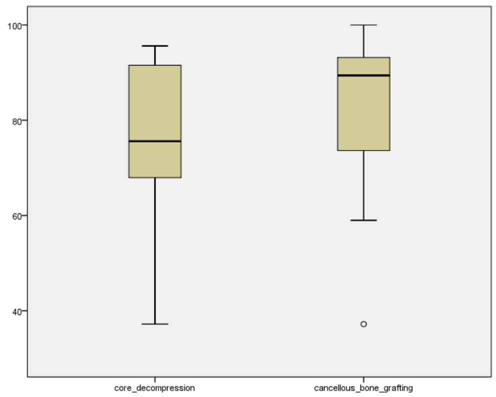


**Figure 18: Box plot HOOS**

As a further evaluation every treated hip was staged according to the ARCO classification, using plane radiographs and MRI. In group 1 there were two hips with an ARCO stadium I, five times stage II and four times stage IV. Leading to a calculated mean ARCO stage of 2.5. In group 2 there were six hips with a stage II and five cases with stage III, also leading to a mean stage of 2.5 (Figure 19).

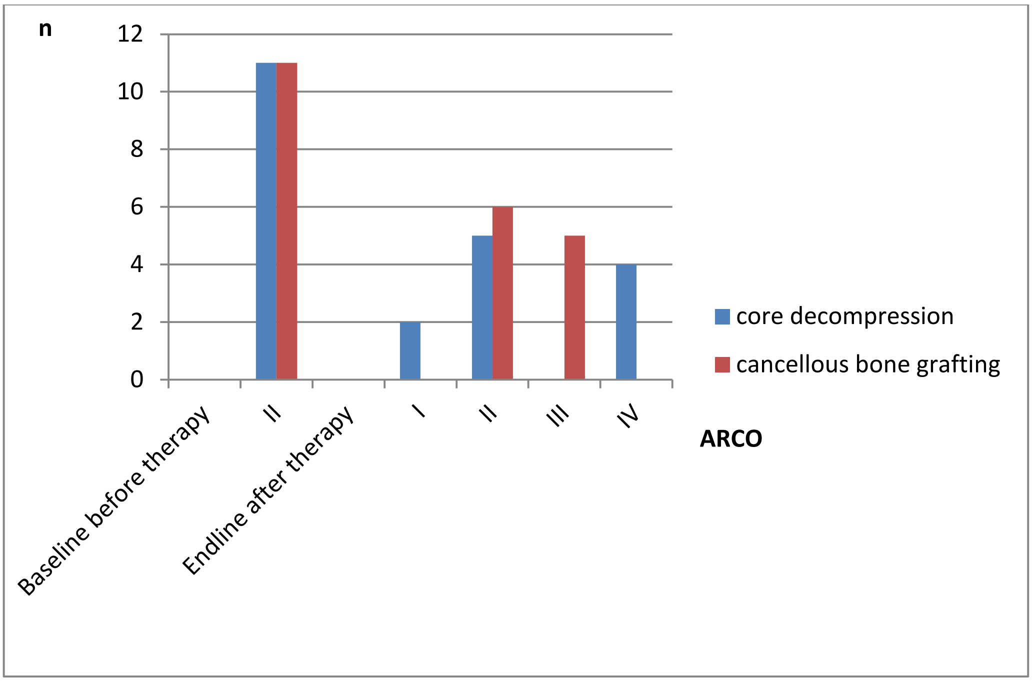


**Figure 19: Distribution of ARCO stages after femoral head preserving therapy (number of cases)**

As both groups only contained patients, who were treated in an ARCO II stage, it shows that in general 13 hips (59.1%) did not progress in the disease. Two of them (9.1%) even improved after the therapy. Six subjects (54.5%) of the cancellous bone grafting group stayed in their initial pre-therapy ARCO stage II. In the core decompression population this could be seen for five patients (45.5%). Two hips (18.2%) of the core decompression group could be diagnosed an improvement to ARCO stage I in the follow up. For the overall group, nine femur heads aggravated to a higher ARCO stage.  Five hips of the cancellous bone grafting group (45.5%) showed a worsening to ARCO III. Four treated hip joints (36.6%) of the CD group deteriorated to ARCO IV with total radiological destruction of the femoral head.

For the evaluation of the conversion cohort (patients who had to get a THR after the initial joint preserving therapy attempt) the different therapy groups were compared according to the time until therapy failure, which was marked by the necessity of THR. There was an overall of 48 patients with a mean time of 10.6 months from joint preserving therapy attempt to prosthetic supply. The core decompression group had a mean success period of 9.5 months (1.3 to 26.8 months, SD 7.0 months). Those treated with CD and cancellous bone grafting showed a mean term of 11.3 months (3.0 to 67.6 months, SD 12.9 months). Statistical analysis of the time period brought forward no significant difference between the two different groups (p=0.54). The four patients treated with Ilomedin infusion came to a mean success time of 11.9 months showing again no statistical relevant benefit in comparison to the two interventions with CD vs. Ilo - (p=0.54) and CBG vs. Ilo (p=0.90).

## 4.2 Three dimensional measurement of drilling precision

After the three dimensional model had been created from the performed MRI, the center points of the necrosis and of the drill hole had to be determined in every of the three coordinate axis. Afterwards the distance between the two center points was measured in millimeters. The values of the distances in every single axis were summed up to a total distance. The volume of the necrosis is given in milliliters (ml). The mean volume of the necrotic area in group A was 7.79 ml ranging from 1.74 ml to 23.68 ml, with a standard deviation of 7.7 ml. The mean necrotic volume in group B was 21.1 ml, with a range from 6.0 ml to 46.2 ml and a standard deviation of 12.4 ml. The added mean distances in group A had a mean of 3.58 mm, ranging from 0 mm to 14.06 mm with an SD of 4.2 mm. The mean distance sum in group B was 3.91 mm, with a range from 0 mm to 15.27 mm and a SD of 4.7 mm (see also table 12).

| Group | Core decompression (A) | Cancellous bone grafting (B) |
|---|---|---|
| **Necrosis (ml)<br>min/max, SD** | 7.79<br>1.74/23.7, 7.7 | 21.1<br>6.0/46.2, 12.4 |
| **Distance (mm)<br>min/max, SD** | 3.58<br>0.0/14.06, 4.2 | 3.91<br>0.0/15.27, 4.7 |

**Table 12: Baseline values of necrosis and deviation (Distance: the mean values of the distances in every single axis were summed up to a mean total distance)**

The evaluation showed in both groups that the necrotic area had been reached by the drilling in all cases. It did not matter how large the necrotic bone area had been. The drilling pin (group A) or the reamer (group B) had at least reached into the defect zone at all times.

The second question was if there is a difference in precision between the drilling with the small pin (core decompression) or the 10 mm trephine (cancellous bone grafting). Statistical analysis showed that there cannot be found a significant difference in the precision (p=0.459) (see figure 20 and table 13).

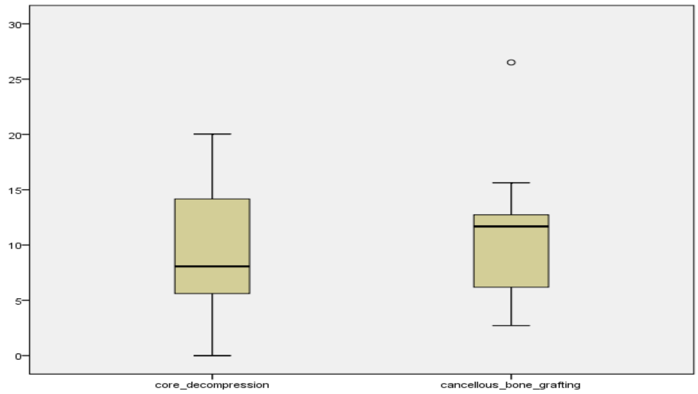


**Figure 20: Box plot precision**

| | CD | CD + CBG |
|---|---|---|
| Mean necrosis in X-axis (mm) min/max, SD | 21.5<br>6.7/40.7; 9.3 | 32.34<br>19.7/45.8; 7.5 |
| Mean necrosis in Y-axis (mm) min/max, SD | 11.01<br>6.6/16.0; 3.7 | 19.15<br>11.5/35.4; 6.4 |
| Mean necrosis in Z-axis (mm) min/max, SD | 26.95<br>13.1/42.0; 11.1 | 30.86<br>17.2/42.2; 7.4 |
| Mean volume of necrosis (ml) min/max, SD | 7.79<br>1.74/23.7; 7.7 | 21.1<br>6.0/46.2; 12.4 |
| Deviation distance in X-axis (mm) min/max, SD | 4.95<br>0.0/12.0; 3.4 | 4.63<br>0.0/11.2; 3.9 |
| Deviation distance in Y-axis (mm) min/max, SD | 1.02<br>0.0/10.2; 3.1 | 0.0<br>0.0/0.0; 0.0 |
| Deviation distance in Z-axis (mm) min/max, SD | 4.77<br>0.0/14.1; 4.8 | 7.13<br>0.0/15.3; 4.9 |

**Table 12: Values of precision measuring (CD: core decompression, CBG: cancellous bone grafting)**

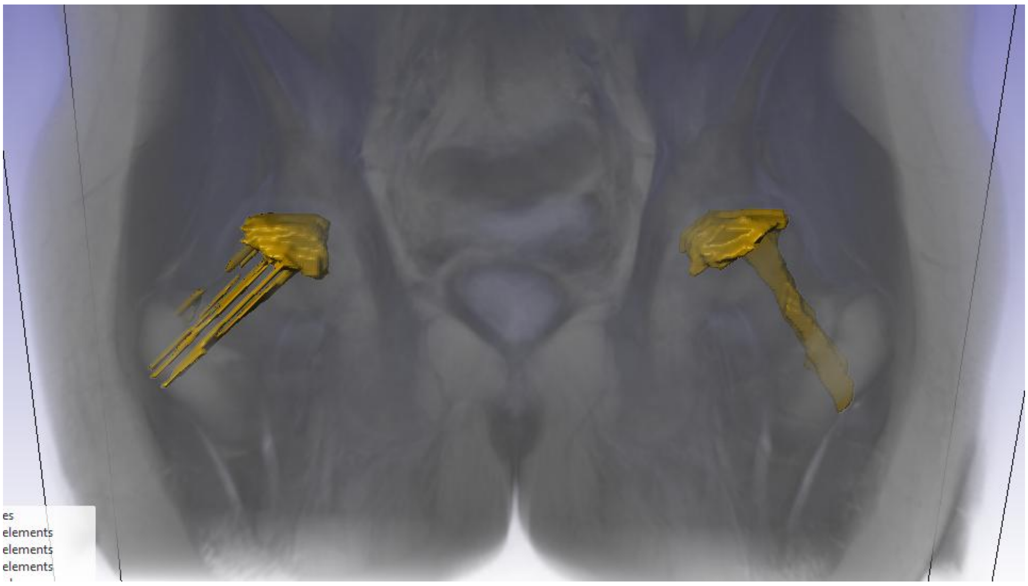


**Figure 21: MRI with three dimensional reconstruction of the necrosis and the drill holes**

Figure 21 shows a three dimensional MRI excerpt of a patient with bilateral femoral head necrosis. On the left side the necrotic area had been drilled with a reamer and cancellous bone grafting. On the right side the necrosis had been drilled with several small pins. The necrosis and the drill holes had been reconstructed as described above (pp. 37-40). It is obvious that in both cases the necrotic area has been hit by the drilling.

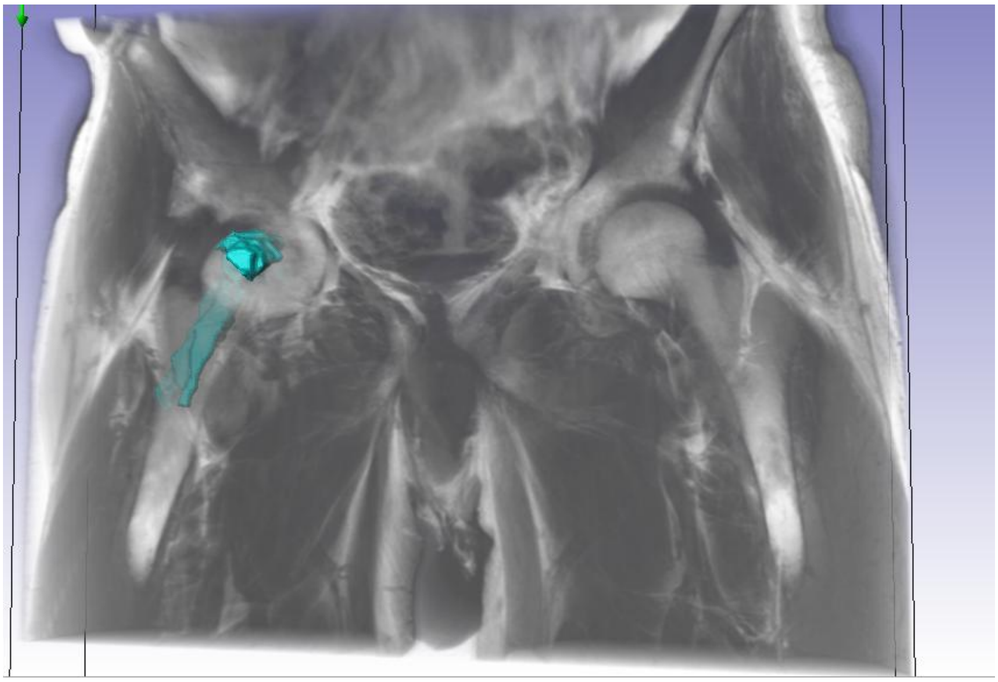

**Figure 22: Patient with cancellous bone grafting**

In figure 22 the necrosis had been treated with cancellous bone grafting. In the right femoral head the necrotic area and the course of the drill hole are reconstructed. The necrosis is in the lateral segment of the femoral head. It can be seen that the surgeon had hit the defect zone with the trephine. The necrosis is measured in every axis, as an example the extent in the z-axis is shown in figure 23.

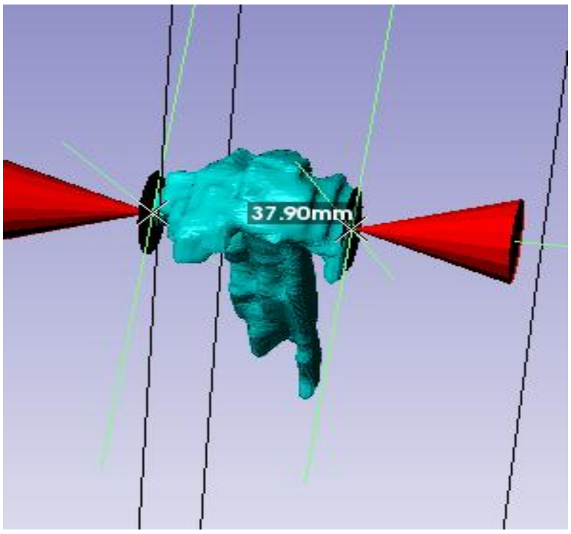


Figure 23: Measurement of necrosis in z-axis

## 4.3 Semiquantitative measurement of bone marrow perfusion

For this part the images, which had been created by dynamic MR sequences had to be measured, as described on the pages (41 to 43). First of all the sick hips that had been treated with any of the joint preserving therapies, core decompression, cancellous bone grafting, Ilomedin infusion or combination of them, were evaluated. The non affected hips were evaluated as well, given there was no THR. For the evaluation the signal increase of the perfusion was calculated. At first there was taken a baseline signal intensity, before the administration of the contrast agent. Thereafter the mean value of the signal intensity of the following three arterial sequences was calculated. With this the percentage signal intensity increase from the baseline intensity without contrast agent to the mean arterial signal intensity with contrast agent was received. All 26 treated hips had a mean signal intensity increase of 26.4%, with a SD of 26.3% and a range from -3.9% to 116.9%.

When split into the different therapy groups (see graphic in figure 24 below), the patients with a combined therapy of core decompression and Ilomedin injection showed the highest increase of the signal intensity (44.41%, SD 28.25%, range from 5.94% to 116.93%). They were followed by the patients with core decompression and cancellous bone grafting (27.62% intensity increase, SD 23.9%, range from 5.59% to 96.48%). The subjects treated with core decompression alone showed a signal intensity rise of 12.42%, standard deviation 11.9% and a range from -3.86% to 31.15%. The group treated with an Ilomedin infusion alone showed a signal intensity increase of 15.31%, SD 9.9%, ranging from 2.93% to 27.22%. The smallest increase was found in the one patient treated with cancellous bone grafting in combination with Ilomedin injection (8.25% increase).

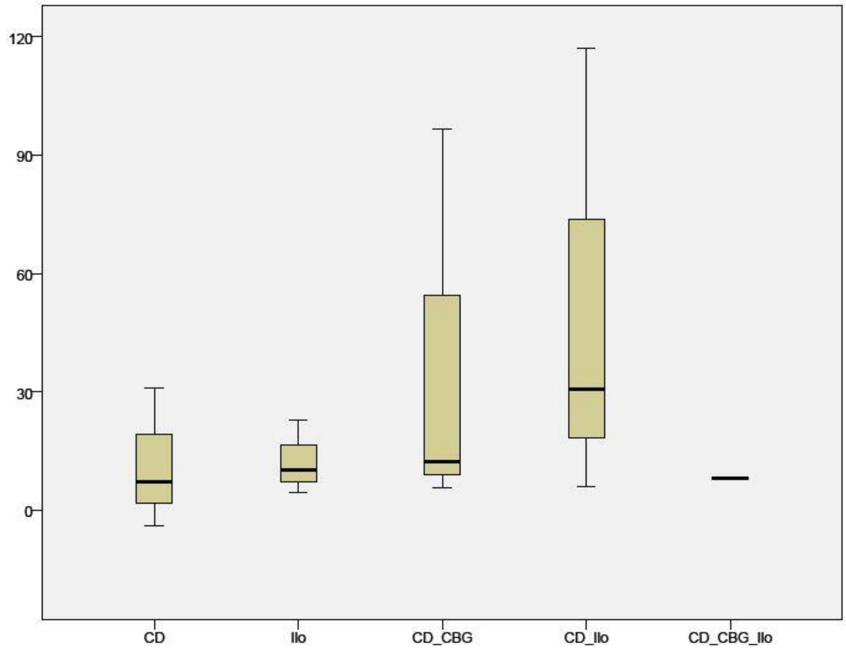


**Figure 24: Box plot signal intensity increase in different treatment groups (CD: core decompression; Ilo: Iloprost infusion; CBG: cancellous bone grafting)**

There were 14 untreated hips. They showed a mean signal intensity increase of 29.42%, with a SD of 27.6% and a range from 4.4% to 114.8%. The box plot below (Figure 25) shows a comparison between the signal intensity increase in the hips, which had a joint preserving treatment of the ONFH, and the contra lateral healthy hip without necrosis and treatment.

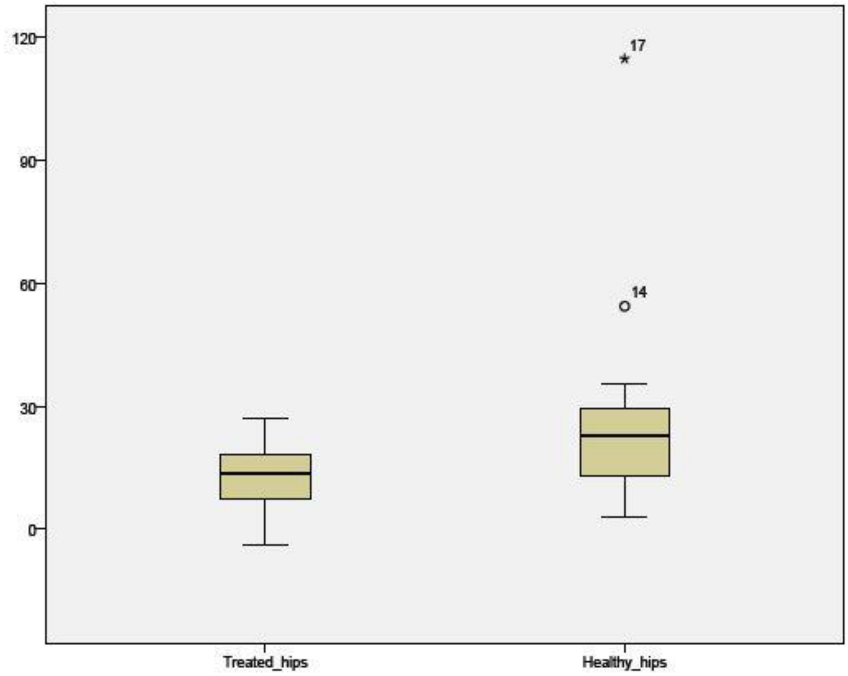


**Figure 25: Signal intensity increase treated and healthy hips**

It showed that there is no statistical relevant difference between the healthy and the treated hips (p=0.86). The split up of the untreated hips shows that patients who had a therapy with the blood flow stimulating Iloprost, have a mean signal intensity increase of 41.4%, whereas patients without a pharmacological therapy had a mean signal increase of 22.7%.

# 5 Discussion

## 5.1 Comparison of core decompression and cancellous bone grafting

Osteonecrosis of the femoral head is a wide spread disease, which is mostly common among young adults. As these patients are mainly in their best years it is not only physically disabling, but it also generates great economic costs. The concerned people often suffer for a long time until they get the right diagnosis. Ohzono et al. found a mean time between the onset of the first symptoms and the initial diagnosis of about eight months, with a range from one month to eight years [83]. The constant pain and the loss of mobility mean an enormous reduction in quality of life. These young patients have great demands on therapy.

This makes it necessary to compare the two most common joint preserving procedures, core decompression and cancellous bone grafting, to clarify which shows better clinical outcome.

Of course it has to be discussed if there are possibilities to prevent the prevalence of ONFH, by avoiding certain risk factors. It is commonly known that smoking and alcohol abuse are very important impact factors on the prevalence of aseptic necrosis [25] [2] [10].

Besides of lifestyle modifications there are also iatrogenic factors, which can influence the risk for aseptic necrosis of any location. Steroids, for example, are very important and powerful drugs in modern medicine. Their use is widely spread, e. g. in transplantation medicine or as immunosuppressives for chronic inflammatory diseases. Physicians should be aware that these medicaments may lead to harmful side effects. It has been shown that a daily dosage of more than 20 mg or a cumulative dose of more than 3 g of prednisolon or its equivalent increase the risk of osteonecrosis [2]. Often these drugs are given for too long or in too high dosage. Mont et al. stated that a dosage of more than 2 g for more than two to three months or a cumulative dose of about 5928 mg prednisolon or its equivalent increases the risk for osteonecrosis significantly [10].

However, there are no general figures about the percentual distribution of cases of ONFH to the mentioned risk factors, but it is stated that about 41% of AVN are due to corticosteroids and about 19% are due to alcohol abuse [70]. Many of the patients show no history of any of these mentioned risk factors but are related idiopathically. This means it is of greatest importance to have efficient therapeutic options.

Although total joint replacement made revolutionary progress during the last few years, it is no good alternative for younger patients. It turned out that the younger the patients are undergoing THR, the worse is the outcome, regarding clinical and subjective results [84]. The lifetime of the prosthesis is significantly shorter than in elder patients. It could be demonstrated that patients undergoing total hip replacement due to osteonecrosis have a reduced bone mineral density [76]. This may lead to premature loosening of the implants [76] [77]. It showed that the etiology of the avascular necrosis has an important influence on the results of hip arthroplasty. It seems that steroid induced necrosis is connected with the highest loosening rates, whereas patients with necrosis after immunosuppressive medication or alcohol abuse suffer higher rates of infections [85].

Younger patients are more active and therefore the strain on the implant materials is higher. This could lead to more aseptic loosening or primary implant failures [86]. The loosening of the materials necessitates repeating surgeries, which have an increased risk of perioperative complications, like bone fractures or infections. But even without extreme physical strain, the implants do not last longer than 10-20 years in average [70]. This means the patients have to undergo two or more revision procedures, which can cause operative difficulties. These problems make it necessary to have reliable joint preserving alternatives, which may at least delay the necessity of total hip replacement.

Besides of conservative methods, mentioned at the beginning, core decompression or cancellous bone grafting are the two most common therapeutic options first described by Ficat and Arlt [9]. These two operative methods are both only for early stages [13] [70]. However, they can be more helpful in further progressed stages than the conservative alternatives. Core decompression is known as a therapy concept for about 60 years [9] [14]. The pathophysiological findings of Ficat and Arlt showed that it is necessary to reduce intraosseous pressure and thereby relief the pain and stop the bone destruction [9]. Another operative therapy is cancellous bone grafting, which is derived from the same pathogenetic approach to reduce intramedullary pressure. In addition to the decompression aspect some authors described that bringing new cancellous bone into the defect area, makes the healing more efficient [73] [74]. The vital bone material is meant to start an intraosseous healing process. It is the conception that the cancellous material contains osteogenitor cells [66] [20]. This surgical technique is widely spread in orthopedic procedures, e. g. when it is necessary to reconstruct small bone lesions in the acetabulum during total hip replacement. Although the mentioned aspects seem to make cancellous bone grafting superior to plain core decompression, there are certain aspects against it [17]. At first the operative effort is larger for cancellous bone grafting. By core decompression the drilling is only performed with thin pins, causing only a small cortical defect. The trephine, which is necessary for bone grafting, removes a bigger part of the lateral cortical bone by insertion. This may cause a structural instability and in consequence a fracture of the collum femoris if a partial load bearing is not complied. Another aspect is the harvest of the cancellous bone. Normally the cancellous bone grafting is performed as a “reversing graft” [74]. This means that the healthy cancellous bone cylinder which lies lateral of the necrosis is removed and filled into the drill channel [16] [15]. However, it showed that there are more potent osteogenetic stem cells in the spongiosa of the iliac crest [87] [88]. So the graft could be taken from there, with disadvantage to a second wound. The iliac crest is very well supplied with blood; in rare cases this may lead to severe bleeding and blood loss. Nevertheless the procedure is well established, documented and common in orthopedic surgery [15] [16].

There is no consent in literature if one therapy is superior to the other, as there are no sufficient stage-related comparisons so far [88] [69].

We saw the necessity to make a comparison between the two procedures. In literature there are almost no comparative studies. Most trials deal with core decompression as a joint preserving therapy [13] [71] [11] [14] [69].

Our results show that there are no significant differences between core decompression and cancellous bone grafting in clinical outcome. Most patients in both groups mentioned only mild **pain** in rest or during physical strain (VAS 3.3 in CD group and VAS 2.2 in bone grafting group (CBG)) with a medium time of 48 months after the therapy in the CD population and about 69.2 months in the CBG group. This means that both interventions can ease the pain. To our knowledge there are no comparable long term pain data (up to almost five years after the initial therapy) in literature available. So we provide data about good long term pain reduction for CD and CBG after femoral head necrosis.

Besides of the pain, **mobility** is of greatest importance for the patients. The extent of movement in every direction was added up as a complete range of motion (ROM) sum. We found only a small difference between the two groups. The cancellous bone grafting subjects showed slightly better results, 224.5° (range from 190° to 265°, SD 24.96) for CD vs. 232.9° (range from 140° to 280°, SD 34.0) for CBG. In none of the functional or lifestyle scores there was a statistical significant difference between the two groups. To our knowledge this is one of the first times that the range of motion has been tested after such a long period of time in such a detailed way. In the most reports in literature about the follow up after therapy of AVN there is only the general description of "clinical improvement" [11] [74] [73]. This is mostly meant as a combination of reduced pain and an improvement in everyday mobility of the hip joint.

Further we performed a retrospective evaluation of the operated hip from clinical standard radiographs. As all included hips were originally staged as ARCO II it is noticeable, that in the bone grafting group there were only "no progression" (ARCO stage II) or a "mild progression" to ARCO III. Whereas in the core decompression group there could be found a progression even to stage ARCO IV. Also in a small amount of cases there was a mild improvement to stage ARCO I. Most cases remained at stage ARCO II. This indicates that the core decompression alone could have a greater progression rate than the bone grafting. However, this is only radiologically and is neither represented in the clinical outcome, nor is it statistically significant.

Last we also performed an evaluation of some clinical scores. Among them were hip specific ones, like the Harris Hip Score and the HOOS, as well as general health scores, like the SF-36 score and the EQ-5D.

The analysis showed that patients with cancellous bone grafting had slightly better results in the hip specific scores (Harris Hip Score: CD 87.7, with range from 58 to 100, SD 13.79 versus CBG 93.2, range from 58 to 100, SD 16.19; HOOS: CD 75.6 range 37.2 to 95, SD 17.71 versus CBG 81.2, range from 37.2 to 100, SD 19.95). But these results were again not statistically significant.

These results are remarkable because of the very long follow up time of about four years in the CD group and even more than five years in the CBG cohort. When compared to data in literature the maximum follow up periods are 12 months. In comparison to these rather short period follow up our patient collective shows very good results regarding to the hip specific scores. In literature 12 months follow up results for the Harris Hip Score of 72.25 to 88.42 are reported [73] [11] [11] [73]. These are encouraging figures for a good long term success after a joint preserving therapy.

In contrast to that the patients with a "normal" core decompression had equal or slightly better results in the general health scores (EQ-5D: CD 79.1, range from 50 to 100, SD 16.25 versus CBG 80.9, range from 60 to 100, SD 16.24; SF-36 physical health: CD 46.6, range from 21.2 to 56.2, SD 9.74 versus CBG 42.3, range from 20.1 to 57.3, SD 12.32; SF-36 mental health: CD 53.2, range from 37.8 to 59.6, SD 5.79 versus CBG 49.8, range from 32.9 to 61.3, SD 12.88).
Compared to figures mentioned in literature the SF-36 results are a bit worse in our population. The mean mental health SF-36 in literature is at about 63.63 to more than 87.53. The physical health aspect of the SF-36 is reported with about 42.77 to 83.13 [11]. It is hard to understand why there is such a discrepancy between the excellent hip specific results and the self assessment of the general health. This might be due to the long time which patients are tainted with the illness.

As a summary it can be stated that both interventions are equal according to the clinical outcome and the subjective perception of the patients. The most important difference between the two procedures is that the cancellous bone grafting is more surgical demanding than core decompression. But when it is performed by an experienced surgeon, there seem to be no increased complication rates. In conclusion it could be stated that more extensive necrotic areas should be treated with core decompression with or without a combined cancellous bone grafting. Smaller lesions should be treated with the less invasive drill or K-wire than a trephine.

This work faces several limitations: first is the rather limited number of subjects. There were only 22 hips included with 11 patients in each of the two groups. But the strongpoint of this part of the study is that we considered only ARCO II stages, in order to avoid a selection bias between the ARCO stages and performed a matching according to age and sex. Earlier publications showed a survivorship for stage II necrosis after core decompression of about 80% for three years of follow up [63].

The above mentioned reasons made it necessary to exclude several patients and led to a reduced number of subjects for our comparison. A further strength is that we matched in this retrospective survey the follow up times for both groups in the range from 26.3 months to 68.5 months in the core decompression group and from 38.0 months to 92.9 months in the cancellous bone grafting group. At last it would be desirable to have a comparison of the baseline clinical scores and pain levels. Surely a prospective study would be the golden standard.

The power of this trial comes from the high level of homogeneity of the two observed groups. The matching according to ARCO stage, sex, age and time after surgery in follow up may equalize any specific differences between male and female patients in each age group. Furthermore, we decided to make a limitation on ARCO II stages. This quite early stage is normally the most common stage when patients are diagnosed first. Earlier publications showed that stage II is the most promising early advanced stage of the disease for joint preserving therapies [60] [14] [63]. Another advantage was that only patients treated by two surgeons were taken into account. By this we minimized the inter-individual differences of the surgical skills. These limitations led to a smaller number of subjects, but also to a high grade of comparability. Besides, the long follow up time of the patients is remarkable. We met the patients on average of 4.6 years after their therapy. This shows that both interventions enable patients a good quality of life, by low pain levels and an almost normal mobility. Also no further progression was seen with a possibly necessity of arthroplasty supply.

However we have to remind that there were patients with a stage II lesion who had to undergo hip arthroplasty after a joint preserving therapy attempt. There were 11 hips with a stage two necrosis that needed THR after a mean period of 9.5 months after core decompression. In the CBG collective there were 14 stage II hips with a failure of the joint preserving attempt after a mean time of 11.3 months. In general it can be seen that 50% of the hips treated with core decompression showed a long term survivorship.

In the cancellous bone grafting group the long term survivorship is at 44%. These results are a little bit worse than those reported in literature, but this may be due to the very long follow up time in our subjects [63] [10].

Another interesting aspect that can be observed is that failure of joint preserving therapies occurs rather early (within one year in our survey). After a progress free time of more than one year, deterioration of the treated hip seems to be more unlikely.

As described above we also took a look at all subjects who did not benefit from the joint preserving therapy. They had to undergo total hip replacement after the failed therapy attempt. However it is not possible to assess how fast this natural destructive course will proceed in the forefront [23]. It is of great importance to delay a necessary prosthetic treatment as long as possible, to save the mostly young patients from repetitive prosthetic surgeries, which are in many cases connected with increased peri-operative risks [76]. For that reason we asked if there was a difference of the time period from the first joint preserving therapy attempt until the performance of THR between the different therapy concepts.

In general there were 48 patients with a mean delay of prosthetic therapy of 10.6 months. The longest time between the joint preserving therapy and the necessity of a final prosthetic treatment could be seen in the four patients only treated with Ilomedin infusion. It was possible to win almost one year (11.9 months) before joint replacement was necessary. This group was followed by core decompression with cancellous bone grafting(CBG) with 11.3 months. The shortest success period was seen for patients after core decompression (CD) with 9.5 months until the joint replacement. But due to our small numbers there was no statistical significance to call one therapy concept superior to the others. The relatively good results of Ilomedin infusion mono-therapy may be due to the small patient number, which means that only selected patients with early stages and mild symptoms have been offered this therapy option. The difference of the progressive free time between the core decompression group and the cancellous bone grafting group is too small as it could be given a recommendation for one of them. Altogether it is not clear why the joint preserving therapies did not work in these patients, in comparison to our main patient collective. Maybe there were certain risk factors or secondary illnesses which had an influence on the therapy. As this survey is a retrospective trial and the patients with conversion to total hip replacement were not re-examined, it is not possible to answer these questions satisfyingly. In order to clarify the risk factors for a therapy failure it is necessary to perform further prospective studies to get more information about the course of the disease and to make it possible to decide which therapy concept fits best for every patient individually.

## 5.2 Three dimensional measuring of drilling precision

For the success of core decompression or cancellous bone grafting it is vital that the necrotic area is hit by the drilling instrument [13]. Only when the sclerotic rim around the necrosis is broken, the intraosseous pressure can be relieved. Although the operative procedure is not easy to perform in some cases, it is of great importance to hit the necrotic zone, in order to stop the progress of the disease [71] [69].

Moreover there is also the risk of complications, like infection or fractures [66]. In the traditional way of core decompression the intraoperative navigation is performed with plain 2-dimensional C-arm imaging. This may sometimes be difficult, because the necrosis is hard to detect on the images and imaging has to be done in different planes to verify the location of the drilling pins [13]. In the last few years intraoperative navigation systems spread and became an alternative operation feature. The technology should help to increase precision of the intervention and to minimize the radiation time [72].

The most important aspect in core decompression seems to be the reduced number of drilling corrections. The directional changes of the pin lead to multiple drilling, which can weaken the femoral neck. This seems to be especially significant for obese patients, because the spatial orientation is more difficult here [71]. Different authors suggest to hit the central part of the necrotic area [71] [72]. Up to now it is not clear if a decentral hit of the necrotic area is also successful because it had not been analyzed yet.

It can be discussed if it is really necessary that the drilling does exactly hit the central point of the necrosis. It seems reasonable that core decompression can also work when the pin hits a decentral part of the necrotic area. It is only crucial that the sclerotic rim distal to the necrotic area is broken up, so intraosseous pressure can be relieved and blood supply can be restored inside the defect zone [9].

In our trial we analyzed if the necrosis was hit by the drilling in every treated subject. As a second question we tried to figure out if there is a difference in precision between core decompression with small pins and one single drilling with a 10 mm trephine as in cancellous bone grafting?

We observed 22 patients with a treatment history of either core decompression or cancellous bone grafting. Ten hips were treated with core decompression, while the other twelve had a cancellous bone grafting therapy. For this analysis there were no limitations, except for a MRI, which could be used for the three dimensional segmentation.

The segmentation and the three dimensional reconstruction of the necrosis and the drill channel showed that in every case the necrosis was hit by the drilling. This means the precondition for a successful intraosseous pressure relieve was given in every observed hip. We found no difference concerning the area or the volume of the necrosis. The necrotic area in the core decompression group had a mean volume of 7.79 ml ranging from 1.74 ml to 23.68 ml. The mean necrotic volume in the bone grafting group was 21.1 ml, with a range from 6.0 ml to 46.2 ml. A possible explanation for the evident volume-difference between core decompression and core decompression with cancellous bone grafting might be the operation procedure. Whereas for core decompression only little drills are hit into the bone and the necrosis, the cancellous bone grafting is connected with a far larger intrusion into the bone architecture. Some authors suggest that the necrotic material has to be removed, leading to a cavity surrounded by healthy bone. Into the resulting hole the healthy cancellous graft has to be inserted [16] [15]. This leads to remodeling processes in the former necrotic area and its surrounding, which let´s the necrosis look larger on the MRI.

For the first part of the analysis we looked if the drill channel or the cancellous graft was within the necrotic volume. This can be seen on MR images, but the spatial position is only identifiable in the three dimensional reconstruction. Figure 26 shows the necrosis and the drill channel in the MRI. On the left side a part of the necrosis and the channel with the cancellous bone grafting is visible. At the right side a small part of the necrotic lesion and faintly the drilling channel are recognizable.

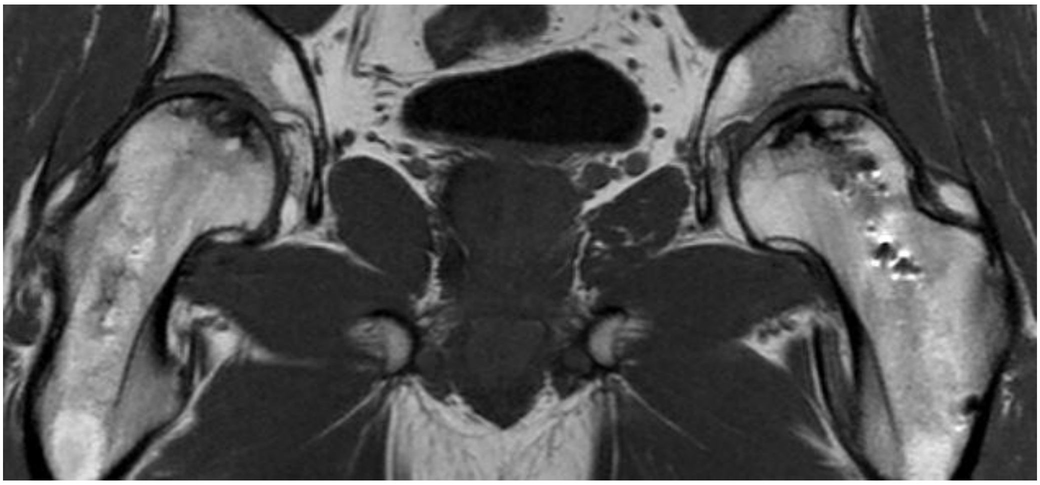

**Figure 26: MRI with bilateral ONFH and cancellous bone grafting**

Figure 27 shows the three dimensional reconstruction of the necrosis and the cancellous bone grafting. The necrosis and the channel, which is necessary for the bone grafting, are reconstructed. In both cases the necrosis is hit by the drilling.

**Figure 27: Three dimensional reconstruction of necrosis and bone grafting**

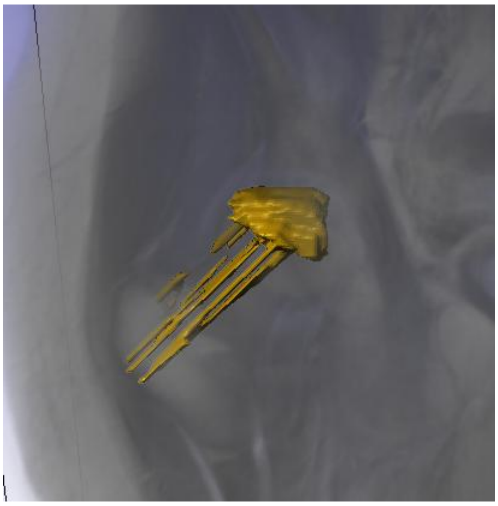

**Figure 28: Reconstruction of multiple drilling CD**

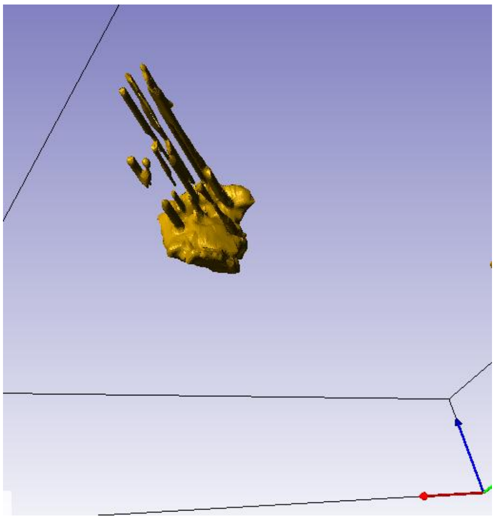

**Figure 29: Reconstruction of multiple drilling CD medial view**

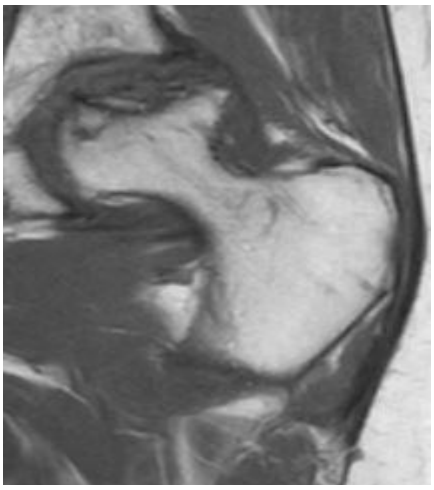

**Figure 30: MRI of necrosis and multiple K-wire drilling**

In the figures 28 and 29 the three dimensional reconstruction of a multiple drilling core decompression is shown. Figure 30 represents the underlying MRI image of the reconstructed K-wire drilling. The necrosis and the multiple drillings are recognizable. It can be seen that the necrotic area has been hit by the drilling several times. The K-wire got into the defect zone in the peripheral part as well as into the central part. This allows a good decompression effect and may induce the formation of new blood vessels. This "microfracturing-effect" may lead to osteogenesis [13]. Nevertheless, a problem of this way of core decompression is the weakening of the cortical bone. As it can be seen in the figures above, the surgeon did not perform the drilling in a fan-shaped way, but with several parallel drillings. Thereby the corticalis had to be penetrated more often. This may lead to an increased risk of insufficiency fractures. However, we have not seen this complication with K-wire technique so far because of partial load bearing postoperatively.

The second question dealing with three dimensional reconstruction and precision measuring was, if there would be any difference in precision between core decompression and cancellous bone grafting. The surgical procedure on the femoral head is basically similar for both. The main difference is that for our bone grafting cases there are used ten millimeter trephines, whereas for core decompression alone only small pins are necessary. The spatial orientation is in both interventions provided by multi-plane radiographic imaging.

For this precisions comparison we set up two groups, group A: core decompression (CD), group B: cancellous bone grafting (CBG).
The first group consisted of ten patients, seven male and three female subjects, with ARCO I or II stages.
In the second group were eleven male and one female patient, with ARCO stage II or III.
After the segmentation and three dimensional reconstructions of the necrotic areas and the drillings, the measuring had been performed as described before (pp.37 to 40).
The results showed that there is no difference in drilling-precision between the two methods. This may lead to the conclusion that the intra- and post-operative risks of a bigger drill channel, as performed for cancellous bone grafting, could be avoided by using only small K-wire pins or a smaller drill. However, one of the main benefits of cancellous bone grafting is the transfer of healthy spongiosa into the necrotic lesion. This aspect is not regarded in this part of the survey.
The mean deviation of the K-wire from the center point of the necrosis in the CD group was 3.58 mm. The mean distance between the central point of the necrosis and the middle of the trephine in the bone grafting group was 3.91mm. This difference was not of statistical significance (p=0.459). This means that although for cancellous bone grafting a bigger drilling instrument is used, there is no significant difference in precision. The rather big deviation of the drilling from the necrosis center point results from the addition of all deviations in every spatial axis to one sum score.
The results of this trial show that the established joint preserving operations, core decompression and cancellous bone grafting, are very precise methods, when performed by experienced surgeons. In our opinion the result of core decompression does only depend on the fact if the necrotic area has been hit or not. **It seems that there is no necessity to get exactly into the center point**. This means it has to be discussed if it is really necessary to install expensive navigation systems, when our results show that all conventionally performed interventions got successfully into the defect zone. Aspects in favor would be a reduction of radiation dose and time for the patients and the surgeons, shorter operation times and easier orientation in obese patients [71]. However, it is necessary to perform further studies in order to answer this question definitely.

This trial shows the comparison of drilling precision for core decompression and cancellous bone grafting. Even more interesting is the use of the modern technology of three dimensional segmentation and reconstruction. This new tool may be established in the future and could be an enormous help for operation planning and performance. In the

special case of ONFH it allows the surgeon an exact spatial imagination of the location and the shape of the necrosis. This may lead to even higher success rates of joint preserving therapies, as the perfect drilling position and direction can be planed pre-operatively. At the moment the manual segmentation is rather elaborate, but with further development the process could be automated.
To our knowledge this is the first study which uses this kind of technology to evaluate the precision of core decompression.

Apart from that we have to state that at least midterm results are the same for core decompression and cancellous bone grafting. But in order to get more valid information about the advantages of either of the techniques more work has to be done. At first studies with longer follow up times are necessary to show long term success rates.

A second topic would be the assessment of the quality of bone healing and mineralization in each treatment group. Is it better in bone grafting cases compared to core decompression, as we would it expect to be? To answer this question a prospective follow up with regular pre- and postoperative bone density measuring would be necessary.

At last we tried to find out if there might be a connection between the size of the necrotic lesion and the progress of the disease. Therefore we compared the ARCO stage of the necrosis before and after the therapy in combination with the lesion´s size. In literature the size of the necrotic area is seen as a possible risk factor for a destructive progress. This is represented in the Kerboul angle or in the sub-classifications A to C which can be added to the ARCO stages [89, 54, 90, 5, 6]. In our trial we do not have the angle or the percentage share of the necrosis on the femoral head, but we have the volume. So we tried to figure out quantitatively if there might be a trend recognizable that a greater volume leads to progress and thus to a higher ARCO stage.

In the core decompression group there were five patients with a necrotic volume smaller than 3 ml (1.74 ml to 2.98 ml). None of them showed a progress in the ARCO staging after the intervention. They all were stage II or better. Three subjects showed an improvement, two stayed stable. The other five patients of the core decompression group had a necrotic volume of more than 3 ml (4.71 ml to 23.68 ml). Four had a progressive course, leading to an ARCO IV stage at the follow-up examination.
In the cancellous bone grafting group we found six patients with a necrosis smaller than 20 ml (6.0 ml to 17.3 ml). Five of them did not progress in ARCO classification (four

times Stage II, one stage III). Only one hip showed a progress from stage II to III. The other six subjects had a necrotic volume of more than 20 ml (22.3 ml to 46.2 ml). Here we observed an aggravation to a higher stage in three cases, a stable course in two patients and an improvement in one hip. The higher volumes in the CBG group can be explained by the intervention itself and the MRI technique. A bigger trephine is used, so there is a larger lesion and the susceptibility artifacts that are shown by MRI are thereby bigger.

The described findings match pretty much the common opinion about the correlation between the size of the necrotic area and the risk of a progressive and destructive course published by Kaushik und Stöve [8] [54]. Although our number of cases is too small to make a statistically significant statement, we take this as a confirmation that it is of great importance for the outcome of the treatment procedure to be performed at an early moment, when the defect zone is still small. Therefore an early and expedient application of diagnostic steps has to be performed. The current golden standard for early diagnosis of osteonecrosis is the MRI. However, there might be possibilities in the future to recognize a disturbed perfusion of the femoral head on the very beginning.

In the following chapter a method is discussed which may be able to provide the possibility to detect the earliest signs of a beginning impairment of the intraosseous blood flow.

## 5.3 Quantitative measuring of femoral head perfusion

This part of the work is based on several publications about the use of dynamic contrast enhanced MRI perfusion measuring of the bone marrow for different diseases of the bone [91] [78]. In this study we took a look at 23 patients with 26 treated hips with a mean of 55 months after therapy. There was no limitation to treatment, ARCO stage or time after therapy.

Several surveys showed that there is a correlation between MRI perfusion signal and microcirculation [92] [93] [78]. However, there are many factors, which can influence

the MRI signal intensity.  Biffar and Bauer were able to proof that perfusion decreases with age and bone marrow fat content. Bauer was able to demonstrate a significant decrease in signal intensity with increasing age in a study with 30 persons with a homogeneous malignant bone marrow infiltration and  94 healthy persons [79] [91].
It has been tried to establish the technique as a diagnostic medium for different bone and soft tissue processes. In musculoskeletal tumors MRI is an acknowledged diagnostic measure. Biffar showed that semiquantitative perfusion measuring could be helpful to differentiate between benign and malignant processes although a clear correlation between increased perfusion and malignant processes could not be found [93].
Another very important field of application is osteoporosis.  It had been shown that a decrease in perfusion measuring is related to a reduced bone mineral density (BMD), which is the pathogenetic correlate of osteoporosis [92] [94]. However, it is not finally clear if the decreased perfusion and the increased osteoporosis risk are due to a reduced blood supply of the bone marrow or due to an increase of bone marrow fat [93] [95].
Another question is, if there is a difference to those patients who had a joint preserving therapy. It has to be asked if there is a correlation between bone marrow perfusion and a process of healing within the bone marrow structure.
In our survey we were able to get the necessary data, as there was made a MR imaging of every patient in the clinical postoperative routine. We found that the method works and can be performed quite easily.

However, we have some limitations: First it is still quite difficult to evaluate the raised data, as we do not have sufficient comparison groups or data, due to lack of subjects in our study, as well as due to missing data in literature.

In their basic work on this topic Saifuddin et all. found that there is a wide range of signal intensity increase in healthy individuals (4.4% to 55.7%) [96]. This makes it quite difficult to compare different treatment groups or even untreated patients with each other.

In order to see if there is a difference in perfusion of the femoral head in patients who have a history of avascular necrosis, it is necessary to establish a control group of subjects with healthy hips. It is questionable if in our patient collective can be found a significant disorder of the perfusion, as everyone of them had a successful joint preserving therapy. As the pathogenesis of femoral head necrosis is meant to be of vascular genesis, the therapy should have improved the microcirculation impairment. As a conclusion this would mean that the improved circulation, represented by physiological perfusion figures, lead to healing processes within the affected bone marrow area [10] [63].

This may lead to the assumption that there should not be found a difference in perfusion between this collective and a control group. However, this is only a theoretical approach. In our study this is supported by the fact that there is no significant difference between the patients´ treated hips and the unaffected contralateral hips (mean signal increase 26.4% versus 29.4%, p=0.86).

The plainest increase in the healthy hip group was found in patients with core decompression in combination with Iloprost infusion (mean signal increase of about 84.6%). The most noticeable fact is that in general there can be observed a serious intensity difference in this group between patients who had a pharmacological therapy with Iloprost to stimulate the blood flow, in comparison to those who had no such infusion. The mean signal intensity increase in the subjects with an infusion therapy was 41.4% versus a 22.7% increase in patients without drug infusion in the follow up. It is possible that the signal intensity increase is due to an improved circulation, as a result of the vaso-active agent.

These results are consistent with reports that Iloprost has a long term healing effect on peripheral circulation in patients with therapy resistant peripheral ulcers [97]. So we could assume that this effect is comparable in avascular necrosis.

In our population we saw a significant better perfusion even 2 to 7 years postoperatively.

Although the Iloprost infusion therapy is currently still an off label therapy, the data above give strong hints for a long term effect on blood flow improvement. Nevertheless there are further studies necessary to prove the impact of the joint preserving therapies on the femoral head bone marrow perfusion.

In addition to that perfusion measuring seems to be a good parameter to identify the vitality of bone marrow in regeneration process within bones. So it could be very useful for further investigation on this topic.

It is also of high interest to analyze the bone marrow perfusion in early preoperative diagnosis of femoral head necrosis. From the postoperative analysis above we can assume a correlation to increased intraosseous pressure, the resulting reduction of intraosseous blood supply and a decrease in bone marrow perfusion measuring. The perfusion measuring might help to detect very early stages of osteonecrosis and pre-necrotic stages as bone marrow edema. The purpose is to detect a possible disrupted perfusion of the tissue and to establish thereby a predictive factor which distinguishes between early progressive stages which have the urge to intervene in the destructive process and those early precursors which are self-limiting [5].

As mentioned in the very beginning of this study the natural course of the disease seems to progress within two to three years to total joint destruction and the necessity for total hip arthroplasty [23].

Because of that it is important to initiate an effective therapy before there is a stage progression or substantial damage of the bone. This would be an important step for patients, as joint preserving therapies are only successful when performed on time. To support and to prove this idea it is necessary to set up further prospective studies, in which bone marrow perfusion measuring is performed on patients with suspected osteonecrosis of the femoral head.

Our work showed that this clinical procedure may bring a great benefit for many patients as it could give hints for disturbances of bone marrow perfusion on a very early stage, by the administration of a contrast agent in addition to a native MRI.

As a general conclusion it can be stated that the statistical results of this survey are limited, due to the rather small patient collective. Nevertheless, one of the main strong points are to show the different application possibilities of modern medicine technology developments, like bone marrow perfusion imaging or three dimensional measuring, in the field of osteonecrosis.

# 6 Summary and Keywords


**Osteonecrosis of the femoral head- a retrospective trial of joint preserving treatment options and a prospect to future clinical possibilities.**

Osteonecrosis of the femoral head is a widespread disease which affects mostly young and active people. Although there are known risk factors, like steroid intake and alcohol abuse the exact pathomechanisms are still unclear. A disturbed blood flow within the bone tissue leads to an increased intraosseous pressure, which itself further reduces intraosseous circulation. Without therapeutic intervention the necrosis proceeds until total hip joint destruction. In order to avoid early hip arthroplasty in young patients, joint preserving therapies are necessary. Mostly common is either a medicamentous therapy with the stable prostacyclin analogon Iloprost, to improve circulation within the bone leading to a restitution of the necrosis or core decompression with or witout cancellous bone grafting. With Core decompression the necrotic area is broken up by drilling into the defect zone with small pins, leading to a relief of the intraosseous pressure. Another option is autologous cancellous bone grafting. Here the necrotic bone is removed by a reamer and replaced by healthy cancellous bone.

As there are little information in literature about long term results of core decompression and cancellous bone grafting we did a follow up survey.

28 Patients with 32 treated hips with a joint preserving therapy at the Department of Orthopedic Surgery, University of Regensburg, during the time from 2006 to 2012 were examined according to a clinical protocol with clinical examination, questionnaires and radiological imaging with X-ray and MRI.

The first part of this study is a comparison between 11 patients with core decompression and 11 patients after cancellous bone grafting. All of them had an initial ARCO II stage. The results showed no significant difference in clinical and radiological aspects four (core decompression) or five years (cancellous bone grafting) after the intervention.

In the second part the precision of the two interventions should be assessed. Therefore a 3D reconstruction of the necrosis and the drilling channels had been performed from MRI images. With the reconstructions it was possible to measure the deviation of the drill channel from the center of the necrotic area exactly. It showed that neither in core decompression nor in cancellous bone grafting the defect zone had been missed. The deviation in both procedures did not differ significantly.

As a third part a prospect on the new technology of bone marrow perfusion imaging was given. Contrast agent enhanced MRI images are performed at defined moments after the application of the contrast agent. With a special ROI (region of interest) measurement it is possible to quantify the signal intensity at each measurement. The increase of the signal intensity is proportional to the intraosseous perfusion. So it gives a correlation to the perfusion in the bone marrow. In this part it could be shown that perfusion imaging is feasible in clinical routine. The exact fields of application and its results have to be discussed in future surveys.

**Keywords:**

Osteonecrosis of the femoral head (ONFH), avascular necrosis (AVN), core decompression, cancellous bone grafting, joint preserving therapy

# 7 References


[1] G. C. Babis, V. Sakellariou, J. Parvizi and P. Soucacos, "Osteonecrosis of the Femoral Head," *Orthopedics 34*, pp. 39-48, 2011.

[2] M. Jay R. Lieberman, M. Daniel J. Bery, M. Michael A. Mont and M. Roy K. Aaron, "Osteonecrosis of the Hip: Management Twenty-first Century," *The Journal of Bone and Joint Surgery,* pp. 834-841, 2002.

[3] M. S. Lee, P.-H. Hsieh, C.-H. Shih and C.-J. Wang, "Non-traumatic Osteonecrosis of the Femoral Head – From Clinical to Bench," *Chang Gung Medical Journal 33*, pp. 351-360, 2010.

[4] M. J. F. Fordyce and L. Solomon, "Early detection af avascular necrosis of the femoral head by MRI," *The Journal of Bone and Joint Surgery 75,* pp. 365-367, 1993.

[5] B. Craiovan, C. Baier, J. Grifka, J. Götz, J. Schaumburger and J. Beckmann, "Das Knochenmarködemsyndrom," *Der Orthopäde 2013 42,* pp. 191-204, 2013.

[6] J. Kramer, G. Scheurecker, A. Scheurecker, A. Stöger, A. Huber and S. Hofmann, "Hüftkopfnekrose," *Der Radiologe 10,* 2009.

[7] D. T. Felson and J. J. Anderson, "Across-Study Evaluation of association between steroid dose and bolus dose and avascular necrosis of bone," *The Lancet,* pp. 902-905, 1987.

[8] A. P. Kaushik, A. Das and Q. Cui, "Osteonecrosis of the femoral head: An update in year 2012," *World journal of oerthopeadics 3,* pp. 49-57, 2012.

[9] R. Ficat, "Idiopathic Bone Necrosis of the Femoral Head," *The Journal of Bone and Joint Surgery B,* pp. 3-9, 1985.

[10] M. A. Mont, L. C. Jones and D. S. Hungerford, "Nontraumatic Osteonecrosis of the Femoral Head: Ten Years Later," *The Journal of Bone and Joint Surgery,* pp. 1117-1127, 2006.

[11] J. Beckmann, T. Schmidt, J. Schaumburger, B. Rath, C. Lüring, M. Tingart and J. Griffka, "Infusion, core decompression, or infusion following core decompression in the treatment of bone edema syndrome and early avascular osteonecrosis of the femoral head," *Rheumatology International 33,* pp. 1561-1565, 2012.

[12] A. Disch, G. Matziolis and C. Perka, "The management of necrosis-associated and idiopathic bone-marrow oedema of the proximal femur by intravenous iloprost," *The Journal of Bone and Joint Surgery 87,* pp. 560-564, 2005.

[13] F. Adrian, B. Deepak, J. Riyaz and H. David, "Long term results of core decompression for ischemic osteonecrosis of the femoral head," *The Journal of Bone and Joint Surgery 76,* pp. 42-49, 1994.

[14] B. H. Kapadia, S. Banerjee, J. J. Cherian and J. Jauregui, "Principles of Core Decompression for Osteonecrosis of the Hip," in *Osteonecrosis*, Springer, 2014, p. 279–284.

[15] J. Grifka and j. P. McAuley, "Drilling and cancellous bone grafting for avascular necrosis of the femoral head," *J.P. Orthop Traumatol 8,* pp. 37-47, 2000.

[16] J. Grifka, "Spongiosa-Umkehrplastik bei Femurkopfnekrose," *Operative Orthopädie und Traumatologie 12*, pp. 40-49, 2000.

[17] D. P. Baksi, "Treatment of osteonecrosis of the femoral head by drilling and muscle-pedicle bone grafting," *The Journal of Bone and Joint Surgery 73,* pp. 241-245, 1991.

[18] J. Beckmann, C. Rader, C. Lüring, B. Rath, J. Grifka and M. Tingart, "Endoprothetische Gelenkversorgung bei Hüftkopfnekrose.," *Osteologie,* pp. 1-7, 2010.

[19] M. W. Hungerford, M. A. Mont, R. Scott, C. Fiore, D. S. Hungerford and K. A. Krackow, "Surface Replacement Hemiarthroplasty for the Treatment of Osteonecrosis of the Femoral Head," *The Journal of Bone and Joint Surgery,* pp. 1656-1657, 1998.

[20] M. T. Houdek, C. C. Wyles, J. R. Martin and R. J. Sierra, "Stem cell treatment for avascular necrosis of the femoral head: current perspectives," *Stem cells and cloning: advances and applications 7,* pp. 65-70, 2014.

[21] M. Sakaguchi, T. Tanaka, W. Fukushima, T. Kubo and Y. Hirota, "Impact of oral corticosteroid use for idipathic osteonecrosis of the femoral head: a nationwide multicenter case-control study in Japan," *Journal of orthopaedic science: official journal of the Japanese Orthopaedic Association 15,* pp. 185-191, 2010.

[22] M. Lukoschek, H.-G. Simank, D. R. C. Brocai and K. Strauch, "Core decompression in osteonecrosis of the femoral head:risk-factor-dependent outcome evaluation using survivorship analysis," *International Orthopaedics 23,* pp. 154-159, 1999.

[23] A. Roth, J. Beckmann, U. Smolenski, A. Fischer, M. Jäger, M. Tingart, C. Rader, K. M. Peters, S. Reppenhagen, U. Nöth, C. Heiss and U. Maus, "S3-Leitlinie. Teil 2: Atraumatische Femurkopfnekrose des Erwachsenen –

unbehandelter Verlauf und konservative Behandlung," *Zeitschrift für Orthopädie und Unfallchirurgir 153,* pp. 488-497, 2015.

[24] C. Rader, "Transient osteoporosis and osteonecrosis of the femoral head. Risk factors, classification and differential diagnosis," *Der Orthopäde,* pp. 423-429, 2007.

[25] Y. Wang, Y. Li and K. Mao, "Alcohol-Induced Adipogenesis in Bone and Marrow: A Possible Mechanism for Osteonecrosis," *Clinical Orthopaedics and related reseearch Number 410,* pp. 213-214, 2003.

[26] R. L. Cruess, "Cortison-induced avscular necrosis of the femoral head," *The Journal of Bone and Joint Surgery 59,* pp. 308-317, 1977.

[27] K.-H. Koo, R. Kim, Y.-S. Kim, I.-O. Ahn, S.-H. Cho, H.-R. Song, Y.-S. Park and H. Kim, "Risk Period for Developing Osteonecrosis of the Femoral Head in Patients on Steroid Treatment," *Clinical Rheumatology, 21*, pp. 299-303, 2002.

[28] M. J. Thornton, G. O'Sullivan, M. P. Williams and P. M. Hughes, "Avascular Necrosis of Bone following an Intensified Chemotherapy Regimen Including High Dose Steroids," *ClinicalRadiology 52,* pp. 607-612, 1997.

[29] H. Starklint, G. S. Lausten and C. C. Amoldi, "Microvascular obstruction in avascular necrosis-lmmunohistochemistry of 14 femoral heads," *Acta Orthopaedica 66*, pp. 9-12, 1995.

[30] R. S. Weinstein, R. W. Nicholas and S. C. Manaolagas, "Apoptosis of Osteocytes in Glucocorticoid-Induced Osteonecrosis of the Hip," *The Journal of Clinical Endocrinology & Metabolism 85*, pp. 2907-2912, 2000.

[31] Y. Li, L. Yue-Bai and W. Yi-Sheng, "Dexamethasone-induced adipogenesis stromal cell cultures: mechanism of steroid-induced osteonecrosis," *Chinese Medical Journal 119,* pp. 581-588, 2006.

[32] S. Chen, J. Li, H. Peng, J. Zhou and H. Fang, "Administration of erythropoietin exerts protective effects against glucocorticoid-induced osteonecrosis of the femoral head in rats," *International Journal of molecular medicine 33,* pp. 840-848, 2014.

[33] C. A. O'Brien, D. Jia, L. I. Plotkin, T. Bellido, C. C. Powers, S. A. Stewart, S. C. Manolagas and R. S. Weinstein, "Glucocorticoids Act Directly on Osteoblasts and Osteocytes to Induce Their Apoptosis and Reduce Bone Formation and Strength," *Endocrinology 145,* pp. 1835-1841, 2003.

[34] R. S. Weinstein, "Glucocorticoid-induced osteonecrosis," *Endocrine 44,* pp. 183-190, 2011.

[35] R. S. Weinstein, R. L. Jilka, A. M. Parfitt and S. C. Manolagas, "Inhibition of Osteoblastogenesis and Promotion of Apoptosis of Osteoblasts and Osteocytes by Glucocorticoids," *The Journal of Clinical Investigation 102,* pp. 274-282, 1998.

[36] W. Fukushima, T. Yamamoto, S. Takahashi, M. Sakaguchi, T. Kubo, Y. Iwamoto and Y. Hirota, "The effect of alcohol intake and the use of oral corticosteroids on the risk of idiopathic osteonecrosis of the femoral head: A case-controll study in Japan," *The Bone and Joint Journal 95,* pp. 320-325, 2013.

[37] Y. Wang, L. Yin, Y. Li, P. Liu and Q. Cui, "Preventive Effects of Puerarin on Alcohol-induced Osteonecrosis,"

*Clinical orthopaedics and related research466,* pp. 1059-1067, 2008.

[38] S. Okazaki, S. Nagoya, K. Tateda, R. Katada, K. Mizuo, S. Watanabe, T. Yamashita and H. Matsumoto, "Experimental rat model for alcohol-induced osteonecrosis of the femoral head," *International Journal of Experimental Pathology 94,* pp. 312-319, 2013.

[39] K.-H. Koo, J. S. Lee, Y. J. Lee, K.-J. Kim, J. J. Yoo and H. J. Kim, "Endothelial Nitric Oxide Synthase Gene Polymorphisms in Patients with Nontraumatic Femoral Head Osteonecrosis," *Journal of orthopeadic ressearch 24,* pp. 1722-1728, 2006.

[40] K. Matuso, T. Hirohata, Y. Sugioka, M. Ikeda and A. Fukuda, "Influence of Alcohol Intake, Cigarette Smoking, and Occupational Status on Idiopathic Osteonecrosis of the Femoral Head," *Clinical Orthopaedics and Related Research,* pp. 115-123, 1988.

[41] G. R. Hetzel, J. Malms, P. May, P. Heering, A. Voiculescu, U. Mödder and B. Grabensee, "Post-transplant distal-limbbone-marrow oedema: MR imaging and therapeutic considerations," *Nephrology Dialysis Transplantation 15,* pp. 1859-1864, 2000.

[42] A. Adekile, M. Haider, R. Marouf and A. Adekile, "HLA-DRB1 Alleles in Hb SS Patients With Avascular Necrosis of the Femoral Head," *American Journal of hematology 79,* pp. 8-10, 2005.

[43] G. Hadjigerorgiu, E. Dardiotis, M. Dardioti, A. Karantanas, A. Dimitroulias and K. Malizos, "Genetic association studies in osteonecrosis of the femoral head: mini review of

the literature," *Journal of skeletal radiology 10,* 2007.

[44] S. Zimmerman and R. Ware, "Inherited DNA mutations contibuting to thrombotic complications in patients with sickle cell disease," *American Journal of Hematology 59,* pp. 267-272, 1998.

[45] J. M. Hong, T.-H. Kim, H.-J. Kim, E.-K. Park, E.-K. Yang and S.-Y. Kim, "Genetic association of angiogenesis- and hypoxia-related gene polymorphisms with osteonecrosis of the femoral head," *Experimental and Molecular Medicine 42,* pp. 376-385, 2010.

[46] L. Yu-Fen, C. Wei-Ming, L. Yung-Feng, Y. Ruei-Cheng, L. Ming-Wei, L. Ling-Hui, C. Ya-Hui, J. Yuh-Shan, L. Pei-Yu, S. Jih-Shyun, H. Shiu-Feng, H. Kwang-Jen, F. C. S.J., H. Hun-Way, C. Yuan-Tsong and T. Shih-Feng, "Type II Collagen Gene Variants and Inherited Osteonecrosis of the Femoral Head," *The New England Journal of Medicine 352,* pp. 2294-2301, 2005.

[47] K.-H. Koo, I.-O. Ahn, R. Kim, H.-R. Song, S.-T. Jeong, J.-B. Na, Y.-S. Kim and S.-H. Cho, "Bone marrow edema and associated pain in early stage osteonecrosis of the femoral head: prospective study with serial MR images," *Radiology 213,* pp. 715-722, 1999.

[48] N. Sugano, T. Atsumi, K. Ohzono, T. Kubo, T. Hotokebuchi and K. Takaoka, "The 2001 revised criteria for diagnosis, classification, and staging of idiopathic osteonecrosis of the femoral head," *Journal of orthopaedic science 7,* pp. 601-605, 2002.

[49] M. Sakamoto, K. Shimizu, S. Iida, T. Aktta, H. Moriya and Y. Nawata, "Osteonecrosis of the femoral head: A prospective study with MRI," *The Journal of Bone and*

*Joint Surgery 79,* pp. 213-219, 1997.

[50] Y.-M. Kim, H. C. Oh and H. J. Kim, "The pattern of bone marrow oedema on MRI in osteonecrosis of the femoral head," *The Journal of Bone and Joint Surgery 82,* pp. 837-841, 2000.

[51] Y. Takatori, T. Kokubo, S. Ninomiya, S. Nakamura, S. Morimoto and I. Kusaba, "Avascular necrosis of the femoral head: Natural history and Magnetic Resonance Imaging," *The Journal of Bone and Joint Surgery 75,* pp. 217-221, 1993.

[52] M. E. Steinberg, G. D. Hayken and D. R. Steinberg, "A quantitive system for staging avascular necrosis," *The Journal of Bone and Joint Surgery 77,* pp. 34-41, 1995.

[53] M. Schmitt-Sody, C. Kirchhoff, W. Mayer, M. Göbel and V. Jansson, "Avascular necrosis of the femoral head: inter- and intraobserver variations of Ficat and ARCO classifications," *International orthopaedics 32,* pp. 283-287, 2008.

[54] J. Stöve, F. Riederle, S. Kessler, W. Puhl and K. Günther, "Reproduzierbarkeit radiologischer Klassifikationskriterien in der Femurkopfnekrose," *Zeitschrift für Orthopädie und Unnfallchirurgie 139,* pp. 163-167, 2001.

[55] J. Stöve, F. Riederle, W. Puhl and K. Günther, "Prädiktoren des Behandlungsverlaufes nach Umstellungsosteotomie bei Hüftkopfnekrose," *Zeitschrift für Orthopädie und Unfallchirurgie 139,* pp. 507-511, 2001.

[56] M. Mont, L. Jones, I. Pacheco and D. Hungerford, "Radiographic predictors of outcome of core decompression for hips with osteonecrosis stage III,"

*Clinical Orthopaedics and Related Research 354,* pp. 159-168, 1998.

[57] C.-J. Wang, F.-S. Wang, C.-C. Huang, K. D. Yang, L.-H. Weng and H.-Y. Huang, "Treatment for Osteonecrosis of Femoral Head: Comparison of Extracorporeal Shock Waves with Core Decompression and Bone Grafting," *The Journal of Bone and Joint Surgery 87,* pp. 2380-2387, 2005.

[58] N. Aigner, G. Petje, W. Schneider, R. Meizer, M. Wlk, S. Kotsaris, K. Knahrl and F. Landsiedl, "Bone marrow edema syndrome of the femoral head: Treatment with the prostacyclin analogue iloprost An MRI-controlled study," *Wiener klinische Wochenschrift 117,* pp. 130-135, 2005.

[59] A. Rajpura, A. C. Wright and T. N. Board, "Medical management of osteonecrosis of the hip: a review," *Hip international 21,* pp. 385-392, 2011.

[60] M. Jäger, C. Zilkens, B. Bittersohl, T. Matheney, G. Kozina, D. Blondin and R. Krauspe, "Efficiency of iloprost treatment for osseous malperfusion," *International orthopaedics 35,* pp. 761-765, 2011.

[61] M. Jäger, A. Werner, S. Lendtrodt, U. Mödder and R. Krauspe, "Schmerztherapie bei nicht juvenilen, aseptischen Osteonekrosen," *Schmerz 18* , pp. 481-491, 2004.

[62] R. Meizer, C. Radda, G. Stolz, S. Kotsaris, G. Petje, C. Krasny, M. Wlk, M. Mayerhöfer, F. Landsiedl and N. Aigner, "MRI-controlled analysis of 104 patients with painful bone marrow edema in different joint localizations treated with the prostacyclin analogue iloprost," *Wiener klinische Wochenschrift 117,* pp. 278-286, 2005.

[63] M. A. Mont, J. J. Cherian, R. J. Sierra, L. C. Jones and J. R. Lieberman, "Nontraumatic Osteonecrosis of the Femoral Head: Where Do We Stand Today? A Ten-Year Update," *The Journal of Bone and Joint Surgery. American volume 97,* p. 1604–1627, 2015.

[64] R.-B. Luo, T. Lin, H.-M. Zhong, S.-G. Yan and J.-A. Wang, "Evidence for Using Alendronate to Treat Adult Avascular Necrosis of the Femoral Head: A Systematic Review," *Medical science monitor 20,* pp. 2439-2447, 2014.

[65] M. C. Vulpiani, M. Vetrano, D. Trischitta, L. Scarcello, F. Chizzi, G. Argento, V. M. Saraceni, N. Maffulli and A. Ferretti, "Extracorporeal shock wave therapy in early osteonecrosis of the femoral head: prospective clinical study with long-term follow-up," *Archives of orthopaedic and trauma surgery 132,* pp. 499-508, 2012.

[66] X. Li, X. Xu and W. Wu, "Comparison of bone marrow mesenchymal stem cells and core decompression in treatment of osteonecrosis of the femoral head: a meta-analysis," *International Journal of Clinical and Experimental Pathology 7,* pp. 5024-5030, 2014.

[67] S. K. Tripathy, T. Goyal and R. Kumar, "Management of femoral head osteonecrosis: Current concepts," *Indian Journal of Orthopaedics 49,* pp. 28-45, 2015.

[68] K.-H. Koo, R. Kim, G.-H. Ko, H.-R. Song, S.-T. Jeong and S.-H. Cho, "Preventing collapse in early osteonecrosis of the femoral head- A randomised clinical trial of core decompression," *The Journal of Bone and Joint Surgery 77,* pp. 870-874, 1955.

[69] I. D. Learmonth, S. Maloon and G. Dall, "Core decompression for early atraumatic osteonecrosis of the femoral head," *The Journal of Bone and Joint Surgery 72,* pp. 387-390, 1990.

[70] U. Maus, A. Roth, M. Tingart, U. Maus, A. Roth, M. Tingart, C. Rader, M. Jäger, U. Nöth, S. Reppenhagen, C. Heiss and J. Beckmann, "S3-Leitlinie. Teil 3: Atraumatische Femurkopfnekrose des Erwachsenen - Operative Therapie der atraumatischen Femurkopfnekrose des Erwachsenen," *Zeitschrift für Orthopädie und Unfallchirurgie 153,* pp. 498-507, 2015.

[71] J. Beckmann, J. Goetz, H. Baethis, T. Kalteis, J. Grifka and L. Perlick, "Precision of computer-assisted core decompression drilling of the femoral head," *Archives of orthopaedic and trauma surgery 126,* p. 374–379, 2006.

[72] J. Beckmann, M. Tingart, L. Perlick, C. Lüring, J. Grifka and S. Anders, "Navigierte Anbohrung der Femurkopfnekrose. Experimentelle und klinische Ergebnisse," *Der Orthopäde 36,* p. 458–465, 2007.

[73] S. N. Shah, C. S. Kapoor, M. R. Jhaveri, P. P. Golwala and S. Patel, "Analysis of outcome of avascular necrosis of femoral head treated by core decompression and bone grafting," *Journal of Clinical Orthopaedics and Trauma 6,* pp. 160-166, 2015.

[74] J. S. Kang, K. H. Moon, B.-S. Kim, D. G. Kwon, S. H. Shin, B. K. Shin and D.-J. Ryu, "Clinical results of auto-iliac cancellous bone grafts combined with implantation of autologous bone marrow cells for osteonecrosis," *Yonsei medical journal 54,* p. 510–515, 2013.

[75] H.-G. Simank, D. R. C. Brocai, K. Strauch and M. Lukoschek, "Core decompression in osteonecrosis of the femoral head: risk-factor-dependent outcome evaluation using survivorship analysis," *International Orthopeadics 23,* pp. 154-159, 1999.

[76] B. Craiovan, M. Wörner, G. Maderbacher, J. Grifka, T. Renkawitz and A. Kehmiri, "Difference in periprosthetic acetabular bone mineral density: Prior total hip arthroplasty: Osteonecrosis of the femoral head versus primary osteoarthritis," *Orthopaedics and Traumatology: Surgery and Research 101,* pp. 797-801, 2015.

[77] B. Craiovan, M. Woerner, S. Winkler, H.-R. Springorum, J. Grifka, T. Renkawitz and A. Keshmiri, "Decreased femoral periprosthetic bone mineral density: a comparative study using DXA in patients after cementless total hip arthroplasty with osteonecrosis of the femoral head versus primary osteoarthritis," *Archives of orthopaedic and trauma surgery,* pp. 1-5, 2016.

[78] J. F. Griffith, D. K. W. Yeung, P. H. Tsang, K. C. Choi, T. C. Y. Kwok, A. T. Ahuja, K. S. Leung and P. C. Leung, "Compromised bone marrow perfusion in osteoporosis," *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research 23,* p. 1068–1075, 2008.

[79] A. Biffar, O. Dietrich, S. Sourbron, H.-R. Duerr, M. F. Reiser and A. Baur-Melnyk, "Diffusion and perfusion imaging of bone marrow," *European journal of radiology 76,* p. 323–328, 2010.

[80] M. Mont and D. Hungerford, "Non-traumatic avascular necrosis of the femoral head.," *The Journal of Bone and*

*Joint Surgery 77(3),* pp. 459-474, March 1995.

[81] A. Nilsdotter and A. Bremander, "Measures of Hip Function and Symptoms," *Arthritis Care and Research 63,* pp. 200-207, 2011.

[82] A. Hinz, A. Klaiberg, E. Brähler and H.-H. König, "Der Lebensqualitätsfragebogen EQ–5D: Modelle und Normwerte für die Allgemeinbevölkerung," *Psychotherapie, Psychosomatik, Medizinische Psychologie (Psychother Psych Med) 56,* pp. 42-48, 2006.

[83] K. Ohzono, M. Saito, K. Takaoka, K. Ono, S. Saito, N. Tetushiko and T. Kadowaki, "The Natural History of Nontraumatic Avascular Necrosis of the Femoral Head," *The Journal of Bone and Joint Surgery 73,* pp. 68-72, 1991.

[84] M. Porsch and A. Siegel, "Künstlicher Hüftgelenkersatz bei jugendlichen Patienten mit Hüftdysplasie - Langzeitergebnisse nach über 10 Jahren," *Zeitschrift für Orthopädie und Unfallchirurgie 136,* pp. 548-553, 1998.

[85] B. Fink and W. Rüther, "Teil- und Totalgelenkersatz bei Hüftkopfnekrosen," *Der Orthopäde 29,* pp. 449-456, 2000.

[86] J. Daniel, P. Pynsent and D. McMinn, "Metal-on-metal resurfacing of the hip in patients under the age of 55 years with osteoarthritis," *The Journal of Bone and Joint Surgery 86,* pp. 177-184, 2004.

[87] M. P. M. Rosenwasser, J. P. Garino, H. A. Kiernan and C. B. Michelsen, "Long Term Followup of Through Debridement and Cancellous Bone Grafting of the Femoral Head for Avascular Necrosis.," *Clinical Orthopaedics & Related Research,* 1994.

[88] M. A. Mont, T. A. Einhorn, P. D. Sponseller and D. S. Hungerford, "The trapdoor procedure using autogenous cortical and cancellous bone grafts for osteonecrosis of the femoral head," *The Journal of Bone and Joint Surgery 80,* pp. 56-62, 1998.

[89] J. Stöve, F. Riederle, S. Kessler, W. Puhl and K. Günther, "Reproduzierbarkeit radiologischer Klassifikationskriterien in der Femurkopfnekrose," *Zeitschrift für Orthopädie und Unfallchirurgie 139,* pp. 163-167, 2001.

[90] J. Stöve, F. Riederle, W. Puhl and K. Günther, "Prädiktoren des Behandlungsverlaufes nach Umstellungsosteotomie bei Hüftkopfnekrose," *Zeitschrift für Orthopädie und Unfallchirurgie 139,* pp. 507-511, 2001.

[91] A. Bauer, A. Stäbler, R. Bartl, R. Lamerz, J. Scheidler and M. Reiser, "MRI Gadolinium enhancement of bone marrow: age-related changes in normales and diffuse neoplastic infiltration," *Skeletal Radiology 26,* pp. 414-418, 1997.

[92] J. S. Bauer and T. M. Link, "Advances in osteoporosis imaging," *European journal of radiology 71,* p. 440–449, 2009.

[93] A. Biffar, O. Dietrich, S. Sourbron, H.-R. Duerr, M. F. Reiser and A. Baur-Melnyk, "Diffusion and perfusion imaging of bone marrow," *European journal of radiology 76,* p. 323–328, 2010.

[94] Y.-X. J. Wang, J. F. Griffith, A. W. L. Kwok, J. C. S. Leung, D. K. W. Yeung, A. T. Ahuja and P. C. Leung, "Reduced bone perfusion in proximal femur of subjects with decreased bone mineral density preferentially affects

the femoral," *Bone 45*, p. 711–715, 2009.

[95] Y.-X. J. Wang, Y.-F. Zhang, J. F. Griffith, H. Zhou, D. K. W. Yeung, T. C. Kwok, L. Qin and A. T. Ahuja, "Vertebral blood perfusion reduction associated with vertebral bone mineral density reduction: a dynamic contrast-enhanced MRI study in a rat orchiectomy model," *Journal of magnetic resonance imaging : JMRI 28,* p. 1515–1518, 2008.

[96] S. A., B. K., R. JP. and B. WP., "Bone marrow blood supply in gadolinium-enhanced magnetic resonance imaging.," *Skelettal Radiology 23,* pp. 455-457, 1994.

[97] S. v. Schmiedeberg, S. Artik, T. Assmann, M. Megahed and T. Ruzicka, "Behandlung therapieresistenterakraler Ulzera mit Iloprost," *Hautarzt 55,* pp. 1150-1153, 2004.

[98] M. Mont, L. Jones, I. Pacheco and D. Hungerford, "Radiographic predictors of outcome of core decompression for hips with osteonecrosis stage III," *Clinical orthopaedics and related research 354,* pp. 159-168, 1998.

[99] S. Inoue, M. Horii, T. Asano, M. Fujioka, T. Ogura, M. Shibatani, W.-C. Kim, M. Nakagawa, T. Tanaka, Y. Hirota and T. Kubo, "Risk factors for nontraumatic osteonecrosis of the femoral head after renal transplantation," *Journal of orthopaedic science : official journal of the Japanese Orthopaedic Association 6,* p. 751–756, 2003.

# 8 Lebenslauf

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Ich, Völkl, Korbinian, geboren am 24.02.1991 in Neustadt an der Waldnaab, erkläre hiermit, dass ich die vorliegende Arbeit ohne unzulässige Hilfe Dritter und ohne Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe.

Die aus anderen Quellen direkt oder indirekt übernommenen Daten und Konzepte sind unter Angabe der Quelle gekennzeichnet. Insbesondere habe ich nicht die entgeltliche Hilfe von Vermittlungs- bzw. Beratungsdiensten (Promotionsberater oder andere Personen) in Anspruch genommen.

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Ulm,