Online ISSN: 2249-4618
Print ISSN: 0975-5888

Global Journal

of Medical Research: H

Orthopedic and Musculoskeletal System

Defects of the Knee

Focal Articular Cartilage

Highlights

Acetabular Reconstruction

Anterior Cruciate Ligament

Discovering Thoughts, Inventing Future

VOLUME 14 ISSUE 1 VERSION 1.0

Global Journal of Medical Research: H
Orthopedic and Musculoskeletal System

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Volume 14 Issue 1 (Ver. 1.0)

Open Association of Research Society

Incorporation No.: 0423089
License No.: 42125/022010/1186
Registration No.: 430374
Import-Export Code: 1109007027
Employer Identification Number (EIN):
USA Tax ID: 98-0673427

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USA Toll Free: +001-888-839-7392
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Packaging & Continental Dispatching

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Yearly Subscription (Personal & Institutional):
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Contents of the Volume

Global Journal of Medical Research: H
Orthopedic and Musculoskeletal System
Volume 14 Issue 1 Version 1.0 Year 2014
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals Inc. (USA)
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Nicotine's Influence on Musculoskeletal Healing: A Review Featuring nAChRS and miRNA

By Carlos M. Carballosa, David J. Fernandez-Fidalgo & Herman S. Cheung
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Abstract- Nicotine is the main ingredient of smoking cessation therapies and electronic cigarettes. New to the market, electronic cigarettes, which are not regulated by Food and Drug Administration (FDA), have been marketed as the safe and alternative approach to cigarette smoking. Although containing significantly fewer amounts of toxic chemicals, electronic cigarettes, as well as other nicotine replacement therapies, still present additional health hazards due to significant nicotine exposure. The effects of nicotine exposure on musculoskeletal health have been extensively studied, but the mechanisms behind these effects are still unknown. Current research, however, suggests that these effects are mediated by the nicotinic acetylcholine receptors (nAChRs) of the musculoskeletal system. These receptors, which are activated in the presence of nicotine, undergo conformational changes that eventually alter the ionic permeability of their respective membranes.

Keywords: cigarette smoking, electronic cigarette, nicotine replacement therapies, nicotine, nicotine acetylcholine receptor, wound healing, bone healing, musculoskeletal, microRNA.

GJMR-H Classification: NLMC Code: WE 168, WS 270

Strictly as per the compliance and regulations of:

Nicotine's Influence on Musculoskeletal Healing: A Review Featuring nAChRS and miRNA

Carlos M. Carballosa [α], David J. Fernandez-Fidalgo [σ] & Herman S. Cheung [ρ]

Abstract- Nicotine is the main ingredient of smoking cessation therapies and electronic cigarettes. New to the market, electronic cigarettes, which are not regulated by Food and Drug Administration (FDA), have been marketed as the safe and alternative approach to cigarette smoking. Although containing significantly fewer amounts of toxic chemicals, electronic cigarettes, as well as other nicotine replacement therapies, still present additional health hazards due to significant nicotine exposure. The effects of nicotine exposure on musculoskeletal health have been extensively studied, but the mechanisms behind these effects are still unknown. Current research, however, suggests that these effects are mediated by the nicotinic acetylcholine receptors (nAChRs) of the musculoskeletal system. These receptors, which are activated in the presence of nicotine, undergo conformational changes that eventually alter the ionic permeability of their respective membranes. The results of these actions are linked to changes in cell proliferation, differentiation and microRNA expression.

Keywords: cigarette smoking, electronic cigarette, nicotine replacement therapies, nicotine, nicotine acetylcholine receptor, wound healing, bone healing, musculoskeletal, microRNA.

I. Introduction

According to recent statistics from the Centers for Disease Control and Protection (CDC), the prevalence of tobacco use among Americans is, as of 2011, around 19% (CDC, 2011). Cigarette smoking, which kills nearly 440,000 Americans each year (CDC, 2011), is the leading cause of preventable death worldwide. Awareness of the diseases associated with cigarette smoking was initiated with the release of the 1964 Surgeon General's Report, which celebrates its 50th anniversary this year. In addition to increasing the susceptibility to various cancers, cigarette smoking also adversely affects the musculoskeletal system; increasing the risk of progressive bone diseases (Porter & Hanley, 2001) and delaying wound (Sopori, 2002), fracture (Alemdaroğlu et al., 2009), and bone healing (Krannitz et al., 2009) following traumatic injury.

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The extent of these effects, however, is believed to be dose dependent and also reversible, to a certain degree, following smoking cessation (Sloan et al., 2010; Fusby et al., 2010). Although these health hazards associated with cigarette smoking are well known, additive chemicals, such as nicotine, make it extremely difficult for chronic users to quit.

II. Nicotine

Nicotine is the quintessential compound responsible for an individual's addiction to cigarettes and/or other tobacco-containing substances (Benowitz, Hukkanen & Jacob, 2009). The most widely used source of nicotine comes from the tobacco plant, which is processed to manufacture cigarettes as well as numerous nicotine replacement therapies. Although nicotine is included in all, the specific concentration used within each product varies from company to company. Table 1 displays the nicotine levels for an average cigarette and the most common nicotine-containing products used for nicotine replacement therapies. Individual products also contain unique methods for nicotine deployment. The most common method for the release of nicotine in the human body is through the burning (combustion) of tobacco, such as seen in smoking cigarettes. In smoking cessation products, such as nicotine gum, transdermal patches and inhalers, nicotine is released through alkaline-buffered diffusion mechanisms designed for targeted areas of absorption (skin, mouth, lungs, etc.). Electronic cigarettes, which recently burst into the scene as the "safer" alternative to cigarettes, use vaporization to release nicotine from a liquid solution.

a) Absorption and Metabolism

Nicotine is a weak base (pKa = 8.0) and its rate of absorption is primarily dependent on the pH and surface area of the environment. In acidic environments with smaller surface areas, nicotine does not rapidly cross cell membranes, whereas in alkaline environments with larger surface areas, it is readily absorbed. As a consequence of this, nicotine from cigarette smoke is not readily absorbed in the mouth, but is readily absorbed in the lungs through the alveoli. As a result, about 2.3-3.5 mg of nicotine, which accounts for approximately 80 to 90% of inhaled nicotine, is absorbed during smoking (Benowitz, Jacob & Denaro, 1991). Average blood-nicotine levels in chronic smokers

have been shown to reach 19.0 ± 11.3 ng/ml after the first cigarette and 22.9 ± 11.2 ng/ml after the second cigarette, correlating to 0.117 ± 0.070 μ M and 0.141 ± 0.069 μ M, respectively (Herning et al., 2009). The various forms of nicotine replacement therapies, such as nicotine gum, transdermal patches and inhalers, are buffered to a more alkaline pH to facilitate the absorption of nicotine through cell membranes. As a result, nicotine absorption is slower when compared to smoking cigarettes and the increase in nicotine blood levels is more gradual.

The most common pathway for the metabolism of nicotine is the cotinine pathway, which accounts for 70 to 80% of the nicotine metabolized by the human body (Hukkanen, Jacob & Benowitz, 2005). The remaining amount is exposed to the bodily tissues and the highest affinity for nicotine is seen in the liver, kidney, spleen, and lung, whereas the lowest affinity is seen in adipose tissue (Urakawa et al., 1994). Nicotine also binds to brain tissues with high affinity, and the receptor binding capacity is increased in smokers compared with nonsmokers (Perry et al., 1999). Cigarette smoking itself influences the rate of metabolism of nicotine. Research has found that the clearance of nicotine is significantly slower in cigarette smokers compared with nonsmokers (Benowitz & Jacob, 1993). In support of this observation are two crossover studies comparing the clearance of nicotine in the same subjects when smoking compared with not smoking. After 4 days of smoking abstinence, nicotine clearance was increased by 14% (Benowitz & Jacob, 2000), and after 7 days of abstinence, nicotine clearance was 36% higher (Lee, Benowitz & Jacob, 1987) when compared with overnight abstinence from cigarettes. Because the same enzyme metabolizes nicotine and cotinine, it has been postulated that cotinine might be responsible for the slowed metabolism of nicotine in smokers. In a study in which nonsmokers received an intravenous infusion of nicotine with and without pretreatment with high doses of cotinine, there was no effect of cotinine on the clearance of nicotine (Zevin, Jacob, Benowitz, 1997). Also carbon monoxide at levels and in a pattern similar to those experienced during smoking had no effect on nicotine and cotinine clearance (Benowitz & Jacob, 2000). Further studies must be performed in order to understand the biological mechanisms that control the rate at which nicotine is metabolized by the human body.

III. The Nicotinic Effect on Musculoskeletal Healing

Nicotine is quickly dispersed throughout the body via cardiac circulation, where it is subsequently exposed to a majority of the internal tissues. The effects of nicotine metabolization throughout the body have been studied extensively; however, its implications in regards to musculoskeletal health and repair are still being investigated. The subsequent sections, therefore, aim to summarize the findings of recent scientific experiments investigating the effect of nicotine on the wound and skeletal healing processes. Healing, in general, is a complex process orchestrated by several role players whose ultimate goal is to efficiently restore damaged tissue to its original state. The basic mechanisms behind wound and skeletal healing and the effects of nicotine on these processes have previously been reviewed (Misery, 2004; Martin et al., 2009; Kallala et al., 2013); however, our aim herein is to present recent and human-only-based research.

In order to do so, the following filters and search titles were used when gathering potential publications on the PubMed database (http://www.ncbi.nl-m.nih.gov/pubmed): Publication Dates: 5 Years; Species: Human; Title: (Wound Healing OR Skin OR Soft Tissue OR Blood Vessels AND Nicotine) OR (Bone OR Fracture Fixation OR Fracture Healing OR Osteoblast OR Osteoclast AND Nicotine).

a) Wound Healing

Two of the major role players involved in the wound healing process are fibroblasts and endothelial progenitor cells. Fibroblasts, which produce extracellular matrix as well as collagen, and endothelial progenitor cells, which give rise to the endothelial cells that help form new capillaries, are simultaneously recruited by activated macrophages and cell mediators to the site of injury in order to replace damaged tissues (reviewed in Martin et al., 2009). Although efficient, these cells can become ineffective when exposed to outside factors such as nicotine. Therefore, current therapies, which aim to facilitate regeneration, use chemical agents and growth factors to enhance the number and function of fibroblasts and endothelial progenitor cells.

b) Fibroblast-Based Studies

In 2010, Choi et al. (2010) observed that nicotine increased the expression of early growth response-1 (EGR-1) in cultured human skin dermal fibroblasts (HSDFs) (Choi et al., 2010). The increased expression of EGR-1, which encodes a protein involved in collagen production and skin wound repair, is suggested by Choi et al. (2010) to improve the function of HSDFs, which, in turn, will facilitate the wound healing process. In a later study, Silva et al. (2012) investigated the effects of nicotine on the viability and migration potential of human gingival fibroblasts (HGFs) (Silva et al., 2012). The researchers observed that nicotine had little to no effect on cell viability and cell death, but did stimulate cell migration. Ultimately, however, Silva et al. (2012) concluded that the effect of nicotine on human gingival fibroblasts was not enough to significantly affect the healing potential of these cells. Tinti & Soory (2012), investigating the oxidative effects of nicotine on HGFs and human periosteal fibroblasts (HPFs), determined that the detrimental effects of nicotine oxidation on

wound healing could be reversed by the anti-oxidant glutathione (Tiniti & Soory, 2012).

c) Endothelial-Based Studies

While studying the in vitro effect of nicotine on human umbilical vein endothelial cells (HUVECs), Y.J. Park et al. (2008) observed that nicotine exposure augmented the proliferation, migration and angiogenic potential of HUVECs (Y.J. Park et al., 2008). In 2011, H.S. Park et al. (2011) investigated the acute and chronic effects of nicotine on the proangiogenic activity of HUVECs (H.S. Park et al., 2011). The group looked at the effect of nicotine on several factors including: production of nitric oxide (NO), expression of endothelial nitric oxide synthase (eNOS), cell viability, migration potential and morphology and the results from these experiments can be summarized into two relatable conclusions. The first conclusion is that nicotine, regardless of exposure time, has an affect on the angiogenic activity of HUVECs. This result was supported by the variation in values between non-exposed and exposed groups for all factors. The second conclusion is that the degree of this nicotinic effect is dependent on exposure time. H.S. Park et al. (2011) showed that the production levels of NO and eNOS were significantly higher in acute vs. chronic exposed HUVECs. The migratory function and tubular formation (number and length of circles) of acutely exposed HUVECs was also significantly better when compared to the chronic exposed groups.

d) Combined Studies

In 2011, Laytragoon-Lewin et al. (2011) investigated the effects of pure nicotine on human-derived fibroblasts and endothelial cells (Laytragoon-Lewin et al., 2011). The researchers showed that, compared to the control, nicotine exposure increased the proliferative capacity and altered the morphology of both cell types. In addition, the researchers evaluated nicotine's effect on the expression of 96 well-defined genes common to both cell types, which were grouped into 5 categories: Cell Cycle and DNA Damage, Apoptosis and Cell Senescence, Signal Transduction and Adhesion, Angiogenesis, and Invasion and Metastasis. Surprisingly, nicotine caused a differential expression in 80% of endothelial and 73% of fibroblast genes investigated within an hour of exposure.

e) Skeletal Healing

The dose dependent effect of nicotine is well known and has been recently demonstrated in many of the cells that comprise the skeletal tissues. The process of bone fracture healing is very similar to the process of wound healing. It can be divided into three phases: reactive phase, reparative phase and remodeling phase. During the reactive phase, blood vessels surrounding the fracture site constrict to prevent further bleeding. At the same time, extravascular blood cells form a clot, known as a hematoma, in the fracture site. All the cells within the clot undergo apoptosis, allowing for the migration and proliferation of fibroblast cells within the clot, forming granulation tissue. The fibroblasts create a provisional extracellular matrix for the migration and proliferation of cells necessary for the formation of new bone. Once this phase is complete, the reparative phase begins with the migration, differentiation and proliferation of precursor cells from the periosteum, a connective tissue membrane covering the bone. These precursor cells include mesenchymal stem cells, which differentiate into chondrocytes and osteoblasts, which are responsible for the formation of new cartilage and new bone, respectively. During this phase, various preliminary bone structures are formed by chondrocytes and replaced by osteoblasts (Ham & Harris, 1971). Finally, during the remodeling phase, the preliminary bone structure is reinforced with compact bone. It can take anywhere from 3 to 5 years for the newly formed bone to achieve its original strength (Ham & Harris, 1971). The time frame in which wound healing and bone fracture healing take place depends on a patient's age and general condition, which includes a patient's exposure to nicotine.

f) Chondrocyte and Bone Marrow Stromal Cell-Based Studies

In 2012, Ying & Cheng et al. (2012) demonstrated that nicotine, at concentrations of 0.154μM (25ng/ml), 0.308μM (50ng/ml), and 0.617μM (100ng/ml), caused significant increases in the cellular proliferation and collagen type II expression/production of human derived chondrocytes (Ying & Cheng et al., 2012).

That same year, Ying & Zhang et al. (2012) used a different set of cells, human bone marrow stromal stem cells (BMSCs), to investigate the effects of a higher nicotine dose on the proliferation and collagen type II expression of these cells (Ying & Zhang et al., 2012). In this study, Ying & Zhang et al. (2012) observed significant enhancements of both qualities at lower nicotine doses (1.0μM), but significant impairments at higher doses of (10μM). In addition, Ying et al. also investigated the effect of nicotine on the expression/production of aggrecan; however, no significant changes were noted.

A 2013 study conducted by Shen et al. (2013) also investigated the effects of nicotine on the BMSCs derived from the iliac crest (Shen et al., 2013). Similar to Ying & Zhang et al.'s results (2012), Shen et al. (2013) observed that low doses of nicotine (0.308μM [50ng/ml] and 0.617μM [100ng/ml]) caused significant and sustained increases in the proliferation of BMSCs, significant increases in alkaline phosphatase (ALP) activity, and significant and sustained increases in the expression of ALP and collagen type I. In addition to significantly decreasing all of these effects, higher doses

of nicotine (6.17μM [1000ng/ml]) significantly inhibited cell-mediated calcium deposition, osteocalcin (OCN) expression, and bone morphogenetic protein-2 (BMP-2) expression.

g) Periodontal Ligament Cell-Based Studies

The increased incidences of alveolar bone degenerating diseases, such as periodontitis, have been well documented in smokers and tobacco users alike (S.I. Lee et al., 2012; Bergstrom, 2004; Ojima et al., 2006). The oral cavity is the initial site of toxic exposure for all tobacco-containing products and many nicotine-containing products (e-cigarettes, nicotine gums, and nicotine lozenges). During their use, nicotine remains in the oral cavity for extended periods of time causing a rapid increase in concentration. As a result, the tissues of the oral cavity are extremely susceptible to the effects of nicotine exposure.

A 2009 study by H. Lee et al. (2009), investigating the effects of nicotine on periodontal ligament (PDL) cells, showed that nicotine downregulated the expression of osteoblastic differentiation markers ALP, OCN, and osteopontin (OPN) (H. Lee et al., 2009). In order to prevent additional cytotoxic effects, nicotine decreased the expression of osteoprotegerin (OPG) while simultaneously increasing the expression of receptor activator of nuclear factor-kappa B ligand (RANKL) and the production of transcription factor NF-E2-related factor-2 (Nrf2) and heme oxygenase-1 (HO-1).

A study by S.I. Lee et al. (2012) demonstrated that nicotine exposure promotes endoplasmic reticulum (ER) stress and facilitates extracellular matrix degradation via downregulation of extracellular matrix molecules, such: as collagen type I, elastin, and fibronectin; and upregulation of matrix metalloproteinases (MMPs), including: MMP-1, MMP-2, MMP-8 and MMP-9 (S.I. Lee et al., 2012). Interestingly though, S.I. Lee et al. (2012) demonstrated that these negative effects could be attenuated through the use of the experimental drug Salubrinal and small interfering RNA.

h) Adult Stem Cell-Based Studies

Currently, a majority of the research in this field has shifted its focus towards the effect of nicotine on adult stem cells. This shift is especially important because these cells are the progenitors for many of the bone remodeling cells. Presently, the mesenchymal stem cells (MSCs) derived from the human bone marrow are most investigated population of these cells.

A study by Ruiz et al. (2012) investigated the dose dependent effects of nicotine on the mechanical properties of human bone marrow - derived MSCs (h MSCs) (Ruiz et al., 2012). At 0.5 and 1.0 μM concentrations, nicotine significantly increased the stiffness of the h MSC cytoplasm and nucleus. The authors suggest that this increase in stem cell stiffness reduces the ability to respond to mechanical stimuli and therefore hinders mechano-induction. A stiffer stem cell would also experience retardation in locomotion seeing as it would be less compliant and consequently more likely to encounter difficulties when traveling out of the bone marrow.

In 2012, a study by B. Kim et al. (2012) showed that nicotine had dose dependent effects on human alveolar bone marrow-derived mesenchymal stem cells (hABMMSCs) (B. Kim et al., 2012). The researchers investigated the effect of nicotine (1μM-5mM) on the proliferation of hABMMSCs and observed no changes at low concentrations (1μM-100μM), significant increases at moderate concentrations (1-2mM), and significant decreases at high concentrations (5mM). High concentrations of nicotine also caused significant detrimental effects to cell morphology, ALP activity, calcium accumulation, and osteogenic gene expression. A majority of these effects, including: reduced ALP activity, reduced calcium deposition, and reduced expression of OCN, bone sialoprotein (BSP), collagen type I α 1 (COL1A1), and runt-related transcription factor 2 (Runx2), were observed at the 2mM concentration. These results confirm the dual effects of nicotine and, although not explicitly stated, suggests that the threshold value for positive to negative effects in hABMMSCs exists somewhere in the mM range.

Ng. et al. (2013) also investigated the effects of nicotine on h MSCs as well as PDL-derived stem cells (PDLSC) (Ng et al., 2013). At 1μM, nicotine significantly reduced the proliferation and migration potential of both adult stem cell populations. The osteogenic differentiation potential of h MSCs and PDLSCs was also inhibited by nicotine as made evident by reductions in alkaline phosphatase activity and calcium deposition. Nicotine also significantly downregulated the expression of protein tyrosine kinase 2 (PTK2), a gene associated with cell migration, and also downregulated the osteogenic genes RUNX2, alkaline phosphatase (ALPL), osteocalcin (BGLAP), COL1A1 and collagen type I α 2 (COL1A2). Ng et al. (2013) also were the first to demonstrate that nicotine had a dose dependent effect on the microRNA (miRNA) expression profiles of PDLSCs. Moreover, the authors noted that half of the top 10 differentially expressed miRNAs were related to osteogenesis.

These recent studies continue to demonstrate the potent effects of nicotine on musculoskeletal tissue regeneration. Whether direct or indirect, the effects of nicotine exposure appear to be beneficial at low concentrations, but detrimental once concentrations exceed a certain threshold. Most studies aim to investigate the effects of nicotine at physiological concentrations with hopes of identifying these cell-specific threshold values; however, a majority of these studies tend to investigate vast concentration ranges that fall outside of the normal. This approach further

demonstrates the lingering uncertainty surrounding the exact effects of nicotine exposure in the musculoskeletal system and throughout the body. Although numerous studies detail the general effects of nicotine on certain cells, few detail the specific mechanisms behind nicotine's action. Current research, however, points to nicotinic acetylcholine receptors as the main potential mediator of the nicotinic effect.

IV. Nicotinic Acetylcholine Receptors

Once internalized and in the blood stream, nicotine is free to complex with a subset of cholinergic receptors known as nicotinic acetylcholine receptors (nAChRs). These specific receptors, believed to be the main mediators behind nicotine's cellular effects, have been identified on numerous cellular populations including, but not limited to: epithelial cells, keratinocytes, vascular endothelial cells, osteoblasts, embryonic stem cells and mesenchymal stem cells (Chemyavsky et al., 2005; Resende et al., 2008; Wang et al., 2010; Wessler & Kirkpatrick, 2008; Macklin et al., 1998; Walker et al., 2001). NAChRs are predominantly expressed on neuronal and neuromuscular tissues (Picciotto et al., 2001) and serve to regulate the flow of specific ions across these membranes (Albuquerque et al., 2009). Although all nAChRs serve the same basic purpose, the downstream implications initiated by receptor activation vary from location to location (Boulter et al., 1987; Papke et al., 1989; Papke & Heinemann, 1991; Portugal & Gould, 2008); this variation is partly due to the different interactions that occur with different tissue components, but mostly to the specific combination of subunits that are used to build each nAChR.

To date, 16 unique subunit varieties have been identified in the mammalian species (Dani & Bertrand, 2007; Lukas et al., 1999). Functional nAChRs are created from a specific combination of 5 of these subunits. This combination is dependent on the location of the cell in the body and receptors on these cells are arranged in one of two conformations, homopentameric or heteropentameric (Hurst, Rollema & Bertrand, 2013). In the former arrangement, commonly only seen in neuronal tissues, nAChRs are created using only one subunit type. On the other hand, heteropentameric nAChRs, which exist in a wider variety of tissues, are created using a mix of subunit varieties. Although slightly different in function, all subunits used to form functional nAChRs share the same basic structure. Each subunit is divided into three major domains: an extracellular amino acid domain, a transmembrane domain containing 4 individual units (labeled TM1-TM4), and a cytoplasmic domain composed of an amino acid loop (Albuquerque et al., 2009). Although almost entirely consistent amongst subunit varieties, the amino acid sequences of these domains are unique to each subunit. Variations in only a few amino acids are enough to influence receptor features such as agonist binding and ionic preference (Wallace & Bertrand, 2013; Albuquerque et al., 2009; Galzi et al., 1992; Corringer et al., 1999).

Subunits are typically classified as either α- or non-α subtype depending on their amino acid sequence (Albuquerque et al., 2009). To date, 9 nAChR α-subunits have been identified in the mammalian species: α1, α2, α3, α4, α5, α6, α7, α9 and α10 (Albuquerque et al., 2009). α-subunits contain a characteristic cysteine-cysteine bond proximal to TM1 in their extracellular domain, which is critical for agonist binding (Albuquerque et al., 2009). In heteropentameric nAChRs, α-subunits contribute to the "positive" side of the ligand-binding channel and influence the ligand affinity of the receptor (Albuquerque et al., 2009); however, there are two exceptions, the α5 and α10 subunit. Although both subunits are classified as α, neither contributes to the "positive" side of the ligand-binding channel (Albuquerque et al., 2009). On the other hand, the non-α subunits, as well as the α10 subunit, contribute to the "negative" face of the ligand-binding channel and influence the ligand selectivity of the receptor. To date, only 7 different nAChR non α-subunits have been identified in the mammalian species: β1-β4, δ, γ, and ε. Together the α- and the non α- subunits (in the heteropentameric case) align to create a ligand-binding site. When present in sufficient quantities, receptor agonists, such as nicotine, bind to this region and activate the receptor. If closed, receptor activation leads to the opening of the transmembrane ionic channel (reviewed in Albuquerque et al., 2009; Dani & Bertrand, 2007). In this conformation, extracellular ions are free to flow into the intracellular domain. The physiological implications arising from the increase in ionic permeability across the membrane following nAChR activation vary from tissue to tissue (S.Y. Kim et al., 2012; Huang and Winzer-Serhan, 2006; Zia et al., 1997; Villablanca, 1998; Sharma & Vijayaraghavan, 2002); however, for the purposes of this review we will only mention; albeit brief due to the lack of research, the nicotinic receptors of the musculoskeletal system and the potential cellular effects that may arise following receptor activation due to nicotine.

a) Musculoskeletal nAChRs

i. *Muscle Tissue*

Compared to the rest of the body, muscular nAChR expression is relatively basic/straightforward. Muscular nAChRs exist in only one of two heteropentameric conformations, 2α1/β1/δ/γ and 2α1/β1/δ/ε (Albuquerque et al., 2009); however, α4, α5, α7 and β4 subunit transcripts have been identified in early skeletal development (Corriveau et al., 1995). Differing by only one subunit, the two muscular nicotinic

receptors have unique sites of expression and characteristic functions. γ-containing receptors are typically found on immature, non-innervated muscle and are known to have ionic channels that remain open for longer periods of time after receptor activation (Albuquerque et al., 2009). As the muscle begins to develop, the subunit composition of the nAChR will gradual change by replacing the γ subunit with the ε subunit. This process is critical for successful muscle development (Hurst, Rollema & Bertrand, 2013). These new receptors, which aggregate proximal to the axon terminals (Corriveau et al., 1995), are different from their immature counterparts in that they are more susceptible to activation by receptor agonists (Conti et al., 1994; Lindstrom, 1997; Missias et al., 1996). As a result, ε-containing nAChRs can be activated more rapidly and with lower concentrations of receptor agonists. The receptors inherently gate both Na+ and Ca2+ ions; however, the higher permeability lies with Na+ (Albuquerque et al., 2009). In the muscular case, the activation of nAChRs typically causes an inward flux of Na+, which depolarizes the membrane (Fagerlund & Eriksson, 2009) and releases intracellular Ca2+.

ii. *Bone Tissue*

H MSCs play an integral role in maintaining and repairing many tissues of the musculoskeletal system. Research within the last decade has revealed that, like many other tissues, h MSCs exhibit various nAChR subunits and are therefore susceptible to the nicotinic effect. In a 2009 study, Hoogduijn et al. (2009) screened MSC cells collected from the femoral head for the presence of nAChR subunits. Out of the 7 subunits investigated via RT-PCR (α3, α5, α7, α9, α10, β2 and β4), 3 (α3, α5, and α7) were identified (Hoogduijn, Cheng & Genever, 2009). In addition, Hoogduijn et al. (2009) showed that intracellular calcium stores increased following in vitro treatment with 10μM nicotine. Schraufstatter et al. (2009) obtained similar results when treating hMSCs with a 2μM concentration of nicotine, but further showed that the intracellular calcium flux occur directly through α7 homopentameric nAChR channels (Schraufstatter, DiScipio & Khaldoyanidi, 2009). Contrary to the Hoogduijn et al. (2009) report, Schraufstatter et al. (2009) conducted RT-PCR for 13 nAChR subunits: α1, α2, α3, α4, α5, α6, α7, α9, α10, β1, β2, β3 and β 4 and identified levels for all except α6, α10, and β1. More importantly, however, protein levels for α7, β2, and β4 were identified in these cells, indicating that subunits capable of interacting with nicotine were in fact translated from mRNA transcripts.

Excluding the hMSC population, only four nAChR subunits have been identified within the human bone tissue. It is possible that the typical 5 subunit-based nicotinic receptors do not exist in these tissues, however this cannot be said with certainty seeing as the research in this field is relatively new and thus much has yet to be discovered. In 1997, Romano et al. (1997) identified the α7 n AChR subunit in the periosteum of human bone samples (Romano et al., 1997). This finding is particularly interesting because in general, the α7 subunit is capable of forming homopentameric nAChRs like those seen in neuronal tissues. Shortly after Romano's discovery, Walker et al. (2001) identified the presence of the α4 nAChR subunit within the core of the human bone and in osteoblast cells (Walker et al., 2001). Moreover, Walker et al. (2001) observed that osteoblast proliferation was improved following low doses of nicotine, but unaffected once D-tubocurarine (a known nAChR antagonist) was introduced, suggesting that the α4 nAChR subunit could be a mediator of this process. Most recently, En-Nosse et al. (2009), also working with human osteoblasts, identified both α3 and α5 subunits in human bone tissues (En-Nosse et al., 2009), bringing the total nAChR subunit expression in bone to only 4 α subunits. As previously mentioned, heteropentameric nAChRs require non-α subunits in order to create functional ligand-binding sites. Therefore, in their absence, the effects of nicotine on bone cells would only be possible via homopentameric nAChRs.

iii. *Ligament Tissues*

To date, the only nAChR subunits identified in human ligament tissues are α7 and β4. Wang et al. (2010) was the first to identify the expression of any nAChR on human ligament tissues when they identified the α7 subunit on cultured periodontal ligament cells (PDLs) (Wang et al., 2010). In addition, Wang et al. (2010) observed that nicotine treatment caused an increase in receptor subunit expression, whereas treatment with alpha-bungarotoxin, a specific α7 receptor antagonist, reversed these effects. In 2012, S.Y. Kim et al. (2012) later confirmed the expression of α7 nAChRs in human ligament tissue and also identified the presence β4 nAChR subunit, while investigating the apoptotic effect of nicotine on periodontal ligament derived stem cells (S.Y. Kim et al., 2012). In addition to identifying these subunits, S.Y. Kim et al. (2012) showed that the gene expression of both subunits was upregulated in the presence of nicotine. Moreover, the apoptotic effect observed in the presence of nicotine was reversed once nAChR antagonists were introduced. This research hints at the importance of nAChRs in the ligament and further supports the overarching notion that nicotine can influence cellular physiology via nicotinic receptors.

iv. *Cartilage Tissues*

To date, the only human cartilage tissue investigated for the presence of nAChRs is that of the human growth plate chondrocytes. A study preformed by Kawakita et al. (2008) revealed that chondrocytes cultured from extra human fingers expressed homopentameric α7 nAChRs (Kawakita et al., 2008). In

the presence of nicotine, these chondrocytes experienced diminished matrix production and inefficient hypertrophic differentiation; an affect that was prevented in the complementary murine models when using the α7 nAChR specific antagonist methyllycaconitine. However, until the "preventative" effect of MLA is translated into the human samples of this study, it cannot be definitively stated that the negative effects of nicotine were mediated via the nAChRs of the chondrocytes.

V. Conclusion

The detrimental health effects associated with cigarette smoking are well known. Although many people are aware of these consequences, millions continue to use tobacco-based products on a daily basis. Individuals who try to quit smoking, however, usually do so with the assistance of nicotine replacement therapies that help them gradually overcome their addictions to nicotine. Although not labeled as such, the electronic cigarette is quickly becoming the most popular of the nicotine replacement therapies. These devices simulate regular cigarettes, but use only vapor to deliver nicotine doses. New to the market, ecigarettes, which are not regulated by the Food and Drug Administration, have been marketed as "a safe alternative" to cigarette smoking. Although containing significantly fewer amounts of toxic chemicals, ecigarettes, as well as other nicotine replacement therapies, still present additional health hazards due to significant nicotine exposure.

Nicotine accumulation can occur via chronic smoking and/or the overuse of nicotine replacement therapies. Furthermore, due to its chemical nature, nicotine readily accumulates in some tissues more than others and therefore blood serum concentrations are usually not indicative of the true bodily concentrations (Department of Health and Human Services, 1988). The dose dependent effects of nicotine on human cellular physiology have been, and continue to be, extensively studied. Nicotine's effects, which are typically beneficial at low doses and detrimental at higher doses, are believed to affect numerous cellular processes, including wound and skeletal healing mechanisms (Ma et al., 2011), via ligand-gated nAChRs. In the presence of nicotine, these receptors undergo a conformation change and open their transmembrane ion channels, allowing for ion flow across the membrane. The intracellular flow of ions is believed to influence several secondary messenger signaling pathways (Kihara et al., 2001; West et al., 2003; Brunzell, Russell & Picciotto, 2003; Miñana et al. 1998; Meyer, Gahring & Rogers 2002); however, relationships between these pathways and their effect on the musculoskeletal system have yet to be established.

Nicotine exposure has also been shown to affect miRNA expression (Ng et al., 2013). miRNA are small, non-coding RNAs (~22 nucleotides), which can alter gene expression by forming complimentary base pairs with mRNA strands (Bartel, 2004). These miRNA are expressed throughout the body, including in muscular and skeletal tissues, and have been shown to affect cell viability, cell differentiation and even organ development by downregulating the genes associated with these biological processes (Callis, Chen & Wang, 2007). Each miRNA can target several genes, and therefore upregulation of a single strand can affect various biological processes. A link between the nicotinic effect and the miRNA expression has yet to be fully determined; however, there does appear to be a correlation between the two. In addition, it would also be interesting to see if miRNA expression was also altered as a consequence of nAChR activation. If so, a variety of therapeutic approaches, such as anti-sense miRNA or nAChR antagonists, could be devised to reverse and combat the negative effects of nicotine exposure on biological processes, such as wound and skeletal healing.

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Table 1 : The above table displays the nicotine levels for the most common nicotine-containing products along with the corresponding levels of blood nicotine absorption

Brand	Nicotine Concentration	Absorbed Nicotine
Average Cigarette	13-19 mg (Wynn et al. 2012)	2.3-3.5 mg (Benowitz, Jacob & Denaro, (1991))
NicodermCQ (Nicotine Patch)	7 mg (http://www.nicodermcq.com/nicotine-patch/how-to-use)	not available
	14 mg (http://www.nicodermcq.com/nicotine-patch/how-to-use)	not available
	21 mg (http://www.nicodermcq.com/nicotine-patch/how-to-use)	14.28 mg (Prather et al., 1993)
Nicorette (Nicotine Gum)	2 mg/piece (http://www.nicorette.com/nicorette-gum)	1.56 mg (Benowitz et al., 1988)
	4 mg/piece (http://www.nicorette.com/nicorette-gum)	2.2 mg (Stevens, 1994)
Nicotrol (Nicotine Inhaler)	10 mg cartridge; 4 mg delivered (http://www.pfizer.com/files/products/uspi_nicotrol_inhaler.pdf)	2.04-2.24 mg (Molander et al., 1996; Schneider et al., 2001)
Blue Cig (E-Cigarette)	Cartridges ranging from 0 -16 mg/cartridge (http://www.blucigs.com/cartridges)	not available
Halo Cigs (E-Cigarette)	Refill Liquids ranging from 0 - 24 mg/ml (http://www.halocigs.com/e-liquid.html)	4 mg/20min from 20 mg/ml solution (Goniewicz et al., 2013)

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Global Journal of Medical Research: H
Orthopedic and Musculoskeletal System
Volume 14 Issue 1 Version 1.0 Year 2014
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals Inc. (USA)
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Focal Articular Cartilage Defects of the Knee: Current Review

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Abstract- Injuries to the articular cartilage of the knee are common, they have a significant role in degenerative joint diseases, cartilage is unable to regenerate due to its inherent lack of vascular supply. The management of symptomatic focal traumatic articular cartilage lesions of the knee in active individuals remains a substantial challenge. Although many treatment options are currently available, none of them has fulfilled the criteria for an ideal management solution. Treatment decisions should be based on appropriate evaluation and classification of the pathology. This would enable the treating physician to choose whether to perform a repair or a restoration of the articular surface. The current article reviews the nature and types of cartilage lesions in the knee and the management options utilized in their treatment.

Keywords: cartilage defects, knee injury, repair, surgery, microfracture.

GJMR-H Classification: NLMC Code: WE 300

Strictly as per the compliance and regulations of:

Focal Articular Cartilage Defects of the Knee: Current Review

Dr. Sedeek Mohamed Sedeek[α] & Dr. Chadi Ali[σ]

Abstract- Injuries to the articular cartilage of the knee are common, they have a significant role in degenerative joint diseases, cartilage is unable to regenerate due to its inherent lack of vascular supply.

The management of symptomatic focal traumatic articular cartilage lesions of the knee in active individuals remains a substantial challenge. Although many treatment options are currently available, none of them has fulfilled the criteria for an ideal management solution. Treatment decisions should be based on appropriate evaluation and classification of the pathology. This would enable the treating physician to choose whether to perform a repair or a restoration of the articular surface.

The current article reviews the nature and types of cartilage lesions in the knee and the management options utilized in their treatment.

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I. Introduction

Articular cartilage is vulnerable to traumatic injury and subsequent degeneration. These changes are likely related to the limited capacity for cartilage repair, poor vascular supply, and deficiency in terms of the ability of an undifferentiated cell population to respond to insult {1}.

Hyaline cartilage provides the diathrodial joint with a resilient, wear-resistant, low –friction surface with a high compressive stiffness, effectively minimizing peak loads of subchondral bone {2}.

The collagen fibers, those are predominantly responsible for the structure of hyaline cartilage, are highly cross linked by type II, which are highly cross-linked by type IX collagen fibers. Water is the biggest constituent of articular cartilage accounting for 70% to 80% of its total weight [2]. Negatively charged hydrophilic proteoglycans are composed of glycosaminoglycans attached to linear core proteins. The mesh of collagen fibrils and glycoamionglycans inhibits water to a limited degree {2, 3}.

Metabolically active chondrocytes are unique in that they have a relatively low turnover rate and are sparsely distributed within the surrounding matrix maintaining minimal cell to cell contact {4}.

Articular cartilage is further organized into four zones: superficial, intermediate, deep and calcified cartilage zones. Within the superficial zone, chondrocytes appear flat in shape at close proximity to each other and the collagen fibers are aligned parallel to the articular surface. In the intermediate zone, chondrocytes are oblique in shape and collagen fibers are randomly organized in different directions. Deep zone cartilage, however, is characterized by spherical chondrocytes that are arrayed in columns and the collagen fibers are perpendicular to the articular surface. The collagen fibers in the deep zone penetrate through the tidemark into the calcified cartilage to provide structural stability for the articular cartilage on the subchondral bone {5}.

The interaction of the cells, collagen framework, aggrecan, and retained fluid is responsible for complex biomechanical profile and superior loading characteristic of the hyaline cartilage making it difficult to replace or reproduce {4}.

The insult to the articular cartilage can be traumatic or degenerative. Various metabolic factors such as obesity, alcohol abuse, as well as mechanical factors like instability, and joint malalignment are implicated in its etiology {6}. Repetitive compression forces or sudden impacts cause many articular lesions. High shear forces at the subchondral bone junction are especially damaging. The cartilage injuries can be divided into three types: microdamage to the cells without visible damage (bone bruise on MRI), chondral fracture or fracture of the articular surface with subchondral bone penetration {7}.

The treatment of symptomatic focal traumatic articular cartilage lesions of the knee in active individuals remains a substantial challenge. The pronounced growth in athletics participation and increased stress on physical fitness among all age groups contribute to greater expectations regarding the outcome {8}. The goals of surgical treatment are to provide pain relief and improve joint function, thus allowing patients to comfortably perform activities of daily living and potentially maintain or return to higher levels of activity {1}.

Advances in Arthroscopy and the introduction of techniques designed to restore knee articular function through resurfacing have generated considerable interests and research in recent years. Traditional

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surgical methods such as debridement and drilling have come under greater scrutinydue to the recognition that optimal outcome may be associated with restoration of hyaline or hyaline-like articular cartilage. This concept has challenged the clinician to strive for a more complex histological tissue to repair chondral lesions that may be associated with a more durable response to loading over time {4, 9}.

The aim of this study is to assess basic science, indications, advantages, shortcomings and consequences of different procedures of knee articular cartilage surgery.

II. Classification of Cartilage Defects

The classification the articular cartilage injury is needed in order to guide management decisions and understand the pathogenesis of these lesions {10}. Outerbridge in 1960s classified these defects based on their gross appearance during arthrotomies. In grade1 lesions, the articular cartilage is swollen and soft. Grade 2 lesions are characterized by fibrillation, fissures, and cleft less than 1.5 cm in diameter. Grade 3 lesions are characterized by deep fissures extending down to the subchondral bone. Outerbridge grade 4 lesions have erosion of the cartilage to the subchondral bone {11}.

Other classification systems exist that are more comprehensive and take into account factors such as the location of the lesions; however, the Outerbridge classification is the most widely accepted {10}. The International Cartilage Repair Society (ICRS) developed its own classification system to describe more accurately the chondral defects and to allow for uniformity in the research reporting. ICRS grade I lesions include those that demonstrate softening or those with superficial fissures. Grade 2 injuries describe defects that have a depth less than 50 % of the tissue thickness. Grade 3 injuries include defects that have a depth greater than 50% of the tissue thickness. Lastly, IRCS grade 4 lesions are full thickness lesions extending to or through the subchondral bone plate {12}.

III. Diagnosis

Diagnosis of articular cartilage lesions is complex and can be accomplished by a combination of history, clinical examination and radiographic evaluation.

IV. Clinical Presentation

Patients with focal chondral defects of the knee may be asymptomatic. As the articular cartilage is an aneural tissue, the presence of a defect does not necessarily produce pain. Nevertheless, patients with full- thickness chondral defects may demonstrate major limitations in pain and function {13}. Patients with symptomatic chondral defects generally complain of activity related pain located in a region that correlates with the intra-articular location of the defect for tibiofemoral articulation. Patellofemoral lesions generally cause anterior knee pain, worse with prolonged knee flexion or stair climbing. Patients with chondral flaps may also present with mechanical symptoms such as catching or clicking. Thus, it is absolutely vital that the patient to be questioned about the nature and localization of the symptoms {10, 14}.

V. Imaging

Radiographs should include anteroposterior, lateral, Merchant, and 45^0 flexion posteroanterior weight bearing films {15, 16}. Limb alignment is evaluated with full leg-length films. These series of films could show joint space narrowing, osteophytes, cyst formation and subchondral sclerosis, which are consistent with degenerative joint disease; when present, they are considered relative contraindications for the treatment of articular cartilage lesions {17}. Long leg alignment radiographs are used to specify where the mechanical axis lies. If the mechanical axis bisects the affected compartment, realignment may be necessary {17}.

A magnetic resonance image (MRI) is valuable to evaluate the status of the knee ligaments and menisci if it is obscure. The presence of subchondral edema in the area of a chondral defect may signify overload in that region, but it is not always associated with symptoms. Although, MRI is considered as an outstanding tool for evaluation of cartilage injury, a considerable number of chondral lesions may remain undetected until Arthroscopy, especially partial thickness lesions {18, 19}. It has been found that, fat-suppression imaging is more sensitive than standard MRI for detection of abnormalities of the hyaline cartilage in the knee {20}. Furthermore, more recently, specialized fast spin- echo MRI sequences with a high resolution matrix allowed for an exact assessment of articular cartilage in the knee, with little interobserver variability {21}.

The use of bone scanning in the assessment of articular cartilage lesions is still being determined. Joint overload that initiates the increases in osseous metabolic activity of the bone is detectable using scintigraphy. Scintigraphy may be useful in difficult cases in which the source and the clinical importance of periarticular symptoms remain doubt based on the results of the patient's history, physical examination and radiographic studies {22}.

VI. Nonoperative Treatment

Nonoperative treatment includes nonsteroidal anti-inflammatory drugs, viscosupplementation, bracing, weight loss and rehabilitation. These treatments may provide symptomatic relief and have the potential to alleviate some symptoms. Nevertheless, there has been no evidence, to date, that any of these techniques provide structural improvements of the lesions {23}.

VII. Surgical Options

Operative treatment is broadly classified into three categories, namely, bone marrow stimulation (BMS) techniques, cartilage replacement techniques, and cartilage regeneration techniques.

VIII. Bone Marrow Stimulation (BMS) Techniques

The principle behind bone stimulation procedures is that penetration of the subchondral bone plate leads to bleeding and fibrin clot formation within the chondral defect. Pluripotent, marrow-derived mesenchymal cells migrate into the clot and allow formation of a fibrocartilaginous repair tissue. This tissue provides a more congruous joint surface, leading to symptomatic improvement in the majority of published reports {24, 25}.

Nevertheless, the resultant fibrocartilagenous repair tissue following bone marrow stimulation technique is composed of predominantly type I collagen. Such a repair tissue lacks the normal histological or biomechanical properties of hyaline cartilage. Therefore, it has an inferior stability to compressive and shear forces and tends to deteriorate with time. Abrasion arthroplasty, drilling and microfracture are the three most common methods utilized to violate the subchondral bone {25, 26}.

Microfracture is the most common procedure, it involves a systemic removal of all covering calcified cartilage with a curette. All loose or marginally attached cartilage should be debrided back to a stable rim to get a perpendicular edge. It is of the essence to success of this procedure to create vertical walls of stable articular cartilage to get a "well shouldered" lesion. This improves the local mechanical environment during healing by reducing shear and compression. A surgical awl is used to create holes placed 2 to 3 mm apart, beginning first at the periphery of the lesion. The holes should not be confluent. The fat droplets can be seen coming from the marrow cavity if the approximate depth (2-4 mm) is reached. Once the procedure is completed, the tourniquet (if inflated) should be released and the pump pressure is reduced. One should see blood and marrow fat droplets coming from each hole {25, 27}.

The postoperative rehabilitation program is paramount to the success of this procedure and requires a period of non-weight bearing for femoral condyle lesions and the use of continuous passive motion for up to 6 weeks postoperatively. Patients with a lesion in the patellofemoral joint wear a brace with a flexion stop of 30^0 to limit patellofemoral contact; weight bearing is permitted {17,26}.

The best outcomes are generally reached when this technique is utilized for patients with relatively small cartilage defects and for those who are not physically demanding on their knees. The procedure may be less suited to the patellofemoral joint or the tibia as it has been shown by Kreuz et al in their study {28}.

Knutsen et al found no difference between the outcomes of microfracture and those of autologous chondrocyte implantation for femoral condyle lesions. Nonetheless, patients with smaller lesions did better with microfracture compared to those with larger lesions {29}. Likewise, Gudas et al reported that among patients with lesions exceeding 2 cm^2 in the central part of the medial femoral condyle , those treated with microfracture had lower clinical outcome scores than did those treated with an osteochondral autograft transplantation{30}.

XI. Substitution Techniques

a) Autologous osteochondral grafts

Osteochondral autograft transfer was first reported by Outerbridge and colleagues in 1995 {31}. Osteochondral autograft transplantation is a transfer of one or more cylindrical osteochondral autografts into the cartilage defects, providing a congruent hyaline cartilage covered surface {32}.

The technique can be performed through a small arthrotomy or entirely arthoscopically. After the lesion is identified, the edges are debrided back to stable, healthy cartilage. The base of the lesion is abraded down to the subchondral bone and the number of grafts needed is determined. The autografts are harvested from the-non-weight-bearing periphery of the femoral trochlea or the margins of the intercondylar notch. The appropriately measured tubular chisel is introduced perpendicular to the donor site.it is important to maintain a perpendicular relationship between the donor graft and the articular surface to create well defined vertical walls in the recipient socket as this facilitates congruent plug placement. The chisel is tapped into the donor site for approximately 15 mm to25 mm. The chisel is removed by careful toggling without rotation in order to avoid breakage of the plug. The graft is then pushed out of the chisel from the osseous end to avoid damage to the harvested cartilage. The donor plug is placed over the recipient site and gently advanced into the defect. It is critical to avoid high loads when inserting the graft as this could damage the chondrocytes. The graft is secured in this press-fit manner, and no further fixation is required. Once all grafts have been introduced, the knee should be moved through a full range of movement to ensure graft congruity with the joint surface and their press -fit stability {23, 32, 33}.

Postoperatively, patients are protected from weight bearing for six weeks with the use of a continuous passive motion machine for six hours per day {1}.

The advantages of ostechondral grafting procedures include being a one stage technique, transplantation of viable hyaline cartilage, and relatively brief rehabilitation period {32}.

The restrictions of this technique include the donor site morbidity and a limited availability of graft that can be harvested, therefore this technique is more suited to small (<4cm^2) lesions. Other potential limitations include differences in orientation, thickness and mechanical properties between donor and recipient cartilage as well as graft subsidence at the surface with postoperative weight bearing {32}.

Donor site healing by natural processes results in filling of the defects with cancellous bone and an overlying cartilage like a cap. Hangody and Kárpáti evaluated the survival of the transplanted hyaline cartilage. The graft undergoes osseous incorporation to the subchondral bone while the transplanted cartilage integrates with the adjacent host articular cartilage with fibrocartilage {34}.

Marcacci et al evaluated 30 patients with full-thickness knee chondral lesions (<2.5 cm) treated with *arthroscopic autologous osteochondral transplantation.* All patients were evaluated at 2- and 7-year follow-up. The International *Cartilage* Repair Society form, and magnetic resonance imaging were used for clinical evaluation. The International *Cartilage* Repair Society objective evaluation showed 76.7% of patients had good or excellent results at 7-year follow-up. In conclusion, the results of this technique at medium- to long-term follow-up were encouraging {35}.

b) Osteochondral allograft transplantation

Osteochondral allograft transplantation is a cartilage resurfacing procedure that involves transplantation of a cadaver graft consisting of intact, viable articular cartilage and its underlying subchondral bone into the defect. The size, depth and location of the defect are crucial factors in tailoring of the donor graft {32}. Osteochondral allograft transplantation provides an alternative for treatment of larger lesions (>2.5 cm^2) or those with significant bone loss. It is commonly a second line treatment option, but can be a first line treatment for high demand patients with large lesions {1,32}.

The allografts can be ''fresh'' or frozen. Fresh grafts are usually maintained at 4°C in standard or enriched culture medium for no more than twenty-eight days, which allows chondrocytes to survive after transplantation. The fresh allografts elicit a minimal immune response, the chondrocytes survive, and the bone is successfully revascularized {1,36}.

Allograft transplantation can be done arthroscopically; however, it is most often performed through a small arthrotomy. The lesion is sized with a template, and a correspondingly sized reamer is used to convert the defect to a circular recipient socket with a uniform depth of 6 to 8 mm. An instrumentation system is used to size and harvest a cylindrical plug from the allograft. The donor graft is drilled through its entire depth with a harvester under irrigation with a normal saline solution. The graft is extracted, and a ruler is used to measure and mark the four quadrants of the graft at the depth of the previously measured recipient sites. The graft is then pressed-fit into the socket after careful alignment of the four quadrants to the recipient site.If the implanted allograft is particularly large, fixation may be augmented with bioabsorbable or metal compression screws {1}. Postoperatively, patients are made non-weight bearing for up to 8 weeks and a continuous passive motion is used immediately after the surgery {17}.

Advantages to the use of osteochondral allografts include the ability to achieve precise surface architecture, immediate transplantation of a viable hyaline cartilage as a single-stage procedure, the potential to replace large defects or even hemicondyles and no donor site morbidity. Limitations of osteochondral allografting include limited graft availability, high cost, risk of immunological rejection, possible incomplete graft incorporation, the potential for disease transmission, and the technically demanding aspects of machining and sizing of the allograft {37}.
Ghazavi et al used *fresh* small-fragment *osteochondral allografts* to reconstruct *post-traumatic osteochondral defects* in 126 knees. At a mean follow-up of 7.5 years, 108 knees were rated as successful (85%) and 18 had failed (15%). The factors related to failure included age over 50 years, bipolar *defects,* malaligned knees with overstressing of the grafts, and workers' compensation cases (38).

x. Cartilage Regeneration Techniques

a) Autologous chondrocyte implantation (ACI)

Autologous chondrocyte implantation was first described in 1994, by Brittberg and colleagues {26}. Autologous chondrocyte implantation is ideal for symptomatic, unipolar, well contained chondral or osteochondral defects measuring between 2 and 10 cm^2 with bone loss of less than 6 to 8 mm.

The first stage of autologous chondrocyte implantation is an arthroscopic evaluation of the size and depth of the focal chondral lesion and a cartilage biopsy. The total volume of the biopsied material should be approximately 200 to 300 mg. The second stage is implantation of the cells. This is done usually no sooner than six weeks after the biopsy. At the time of implantation, the defect is prepared by removing any existing fibrocartilage down to the underlying calcified layer. Vertical walls are created at the periphery of the lesion with the use of a combination of a number-15 blade and sharp ring curets. The walls of the defect are

kept as vertical as possible to allow for suture fixation of the graft.

Care is taken to avoid penetration of the subchondral bone plate, as this would stimulate a fibrous response similar to what seen with the microfracture procedure. Next, a periosteal flap that will cover the cartilage defect is harvested from the proximal medial tibia, 2 to 3 centimeters distal to the pes anserinus insertion. All overlying fat and fascial tissue is removed and an appropriately sized flap, typically oversized by 2 mm, is cut sharply with the tissue carefully elevated from the bony surface. With the cambium, or inner layer, of the periosteal flap facing the defect, it is secured to the surrounding cartilage using 6-0 vicryl suture, with the sutures spaced 2 to 3 millimeters apart. The suture fixation is started at the corners of the flap to allow for appropriate tensioning and a small opening is left superiorly for the injection of the cultured chondrocytes. Fibrin glue is applied to fill the gaps between the sutures, creating a water tight pouch, which is checked with a trial saline injection. With the periosteal pouch prepared, the cultured chondrocyte suspension is injected into the defect,focusing on an even distribution within the periosteal pouch.The superior opening is then closed with 6-0 vicryl suture and is sealed with fibrin glue {10,17}.

Postoperatively, lesions of the femoral condyle are treated initially with minimum weight bearing and continuous passive motion . Lesions of the patella-femoral joint are often allowed for weight bearing as tolerated in extension {10}.

b) Outcomes following ACI

Brittberg and associates {39} reported 2- to10-year outcomes of 244 patients with large grade 3 and 4 chondral defects. They found that at a mean follow-up of 4 years, 90% of patients treated for femoral condylar lesions had good to excellent results. A portion of this cohort was followed for a mean of 7.4 years postoperatively, and their results were found to be stable at this longer term time point, with 84% of the overall cohort having good to excellent results. The authors concluded that if ACI is successful, a long lasting, durable repair is achieved {40}.

Nevertheless, Van Assche et al reported on 67 patients randomized to microfracture or ACI. Follow up at 2 years did not show differences in functional outcome {41}.

Recently, Magnussen et al reviewed five randomized controlled trials comparing ACI, osteochondral autograft transfer and microfracture outcomes. All treatments improved clinical outcome measures compared with preoperative assessment, however, no technique had consistently superior results and no study used non-operative control group. The authors recommended that a large prospective study to be conducted and non-operated control to be included {42}.

XI. Summary

Articular cartilage defects of the knee are common, treatment modalities range from palliative to reparative to restorative techniques. Each management plan has its own advantages and disadvantages, futhermore, to date none of these modalities has fulfilled the criteria for an ideal management solution. Nonetheless, all of these procedures improve the clinical status compared with preoperative state. Decision making is supposed to be guided by the patient's physical and physiological demand status, previously failed treatment, and the location and size of the defect.

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Global Journal of Medical Research: H
Orthopedic and Musculoskeletal System
Volume 14 Issue 1 Version 1.0 Year 2014
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals Inc. (USA)
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Anteromedial Portal Drilling Reduces Posterior Cruciate Ligament Impingement during Anterior Cruciate Ligament Reconstruction

By Christopher S. Lee, Shane M. Davis, Paul Re & John C. Richmond

Abstract- *Background:* Posterior cruciate ligament (PCL) impingement following anterior cruciate ligament (ACL) reconstruction can often lead to post-operative graft instability and loss of knee range of motion.

Purpose: The purpose of this study was to evaluate whether drilling a femoral tunnel through an anteromedial portal led to a decreased incidence of ACL-PCL impingement compared to trans-tibial methods during ACL reconstruction.

Methods: Eight cadaveric knees were evaluated arthroscopically. Femoral tunnels used for ACL reconstruction were then drilled using both an anteromedial portal technique as well as a trans-tibial technique. Qualitative and quantitative comparisons of each technique's ability to center a femoral tunnel in a non-PCL impinging position within the native ACL femoral footprint were then recorded.

Keywords: *ACL; PCL; impingement; anatomic reconstruction.*

GJMR-H Classification: *NLMC Code: WS 270, WE 304*

Anteromedial Portal Drilling Reduces Posterior Cruciate Ligament Impingement during Anterior Cruciate Ligament Reconstruction

Christopher S. Lee [α], Shane M. Davis [σ], Paul Re [ρ] & John C. Richmond [ω]

Abstract- Background: Posterior cruciate ligament (PCL) impingement following anterior cruciate ligament (ACL) reconstruction can often lead to post-operative graft instability and loss of knee range of motion.

Purpose: The purpose of this study was to evaluate whether drilling a femoral tunnel through an anteromedial portal led to a decreased incidence of ACL-PCL impingement compared to trans-tibial methods during ACL reconstruction.

Methods: Eight cadaveric knees were evaluated arthroscopically. Femoral tunnels used for ACL reconstruction were then drilled using both an anteromedial portal technique as well as a trans-tibial technique. Qualitative and quantitative comparisons of each technique's ability to center a femoral tunnel in a non-PCL impinging position within the native ACL femoral footprint were then recorded.

Results: Of eight tunnels drilled through an anteromedial portal, none showed signs of PCL impingement and all were centered in the native ACL footprint. Three tunnels (37.5%) drilled trans-tibially showed signs of potential PCL impingement starting at 90 degrees flexion, and all were displaced superior to the center of the native ACL footprint by an average of 3.25 mm.

Conclusion: Femoral tunnels drilled through an anteromedial portal technique were consistently placed in the center of the ACL femoral footprint, and no potential impingement by the PCL was noted. Femoral tunnels drilled trans-tibially had a tendency to displace superiorly and three showed signs of impinging against the lateral border of the PCL.

Keywords: ACL; PCL; impingement; anatomic reconstruction.

What is known about the subject: Classic approaches to ACL reconstruction have led to PCL impingement and eventual ACL graft laxity.

What this study adds to existing knowledge: Use of the newer anteromedial approach to portal drilling during ACL reconstruction leads to decreased PCL impingement when compared to the trans-tibial approach.

I. Introduction

Posterior cruciate ligament (PCL) impingement following anterior cruciate ligament (ACL) reconstruction can often lead to post-operative graft instability and loss of knee range of motion. Second look arthroscopy studies have demonstrated that this is due to graft laxity caused by a combination of repetitive stress and high graft tension as the ACL presses against the lateral border of the PCL during flexion. 22 Howell et al. reported in a cadaver study that lowering the ACL graft on the "clock-face" resulted in a lower incidence of ACL-PCL impingement.9 He also noted that this femoral tunnel position, which is closer to the center of the anatomic ACL footprint, led to a decrease in graft tension of nearly 50 N.18

Many strategies have been devised to center a femoral tunnel in the anatomic footprint of the ACL. Loh et al. demonstrated improved rotational stability with the femoral aspect of the ACL graft oriented in the 10 or 2 o'clock position rather than the 11 or 1 o'clock position.14 Although the trans-tibial drilling method has been largely successful since its advent, recent evidence has demonstrated that its use often results in overly vertical grafts.2, 12, 16, 17, 23 As a result, to achieve optimal femoral tunnel position, many have abandoned the trans-tibial technique in favor of drilling the femoral tunnel independently using an anteromedial portal technique.3, 6, 21

The purpose of this study was to determine whether drilling method, anteromedial portal versus trans-tibial, affected the incidence of ACL-PCL impingement. In addition, we sought to devise an intra-operative test to help avoid ACL-PCL impingement. We tested the hypothesis that a femoral tunnel located in the center of the native ACL footprint was most consistently attainable through an anteromedial portal drilling technique, and that this method subsequently had a lower incidence of ACL-PCL impingement.

II. Materials and Methods

a) Specimen Selection

Eight (four matched pairs) cadaveric knees were evaluated (N = 8). The knees were obtained from specimens with an average age of 66 years old (range 56 to 74 years old). Inspection at the time revealed that all specimens had intact ACL, PCL, articular surfaces and menisci. None had significant degenerative joint disease. All knees underwent an initial diagnostic arthroscopy and were ranged from 0-120 degrees of flexion. All knees were noted to have no impingement of the native PCL against the native ACL.

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b) Creation of Femoral Tunnels and Evaluation for ACL-PCL Impingement

A 30-degree arthroscope was used to evaluate all knees through a lateral viewing portal and a medial working portal. After debridement of the ACL, a thin layer of the femoral attachment was left. This allowed visualization of the broad native ACL footprint that was defined and evaluated through a full arc of motion. Using a Beeth pin, a mark was placed in the anatomic center of the native ACL footprint via a percutaneous technique (Figure 1). For a single-bundle reconstruction, we considered the center as a point placed slightly anterior to the anatomic AM bundle insertion site, roughly 6 mm anterior to the posterior cortex at the 2-o'clock position for a left knee or 10-o'clock position for a right knee.5 An anteromedial portal technique was then used to create the first femoral tunnel.6 Assuming an average 8 mm graft, an 8mm core reamer was used to drill a femoral tunnel to a depth of 5 mm while keeping the knee in 120 degrees of flexion. The core reamer allowed outlining of the area a tunnel would occupy while preserving bone stock (Figure 2). The resultant tunnel was then observed as the knee was flexed from 0-120 degrees. If the PCL obscured any part of the femoral tunnel, it was assumed that PCL impingement would occur at that point in the arc of flexion. The overlapping of the femoral tunnel by the PCL was referred to as the "Femoral Eclipse Sign" (Figure 3).

The conserved bone stock allowed drilling of a second femoral tunnel in the same knee. This second tunnel was created using a trans-tibial method.15 A standard 8mm tibial tunnel was first made using a tip aiming elbow guide set at 53 degrees. The tunnel originated at a point on the tibial cortex hugging the anterior border of the medical collateral ligament and exited through the tibial plateau 7mm in front of the PCL and two-thirds up the medial tibial spine. A 6mm over-the-top guide was then inserted through the tibial tunnel, across the joint and into position on the femur. The knee was flexed to 90 degrees, and the over the top guide was placed on the femur as close as possible to the center of the anatomic ACL footprint (Figure 1). A guide-wire was then drilled into the femur to 40 mm, and an 8mm core reamer was used to drill a femoral tunnel to a depth of 5mm. The knee was then ranged from 0-120 degrees, and the incidence of whether the PCL obscured the trans-tibially drilled femoral tunnel was recorded.

In addition to recording the incidence of ACL-PCL impingement, the ability of both drilling methods to achieve a femoral tunnel position centered in the anatomic ACL footprint was measured. This was done arthroscopically using the tip of an arthroscopic probe (3mm). Both the magnitude and direction of displacement from the center of the native ACL footprint were measured (Figure 1).

c) Statistical Analysis

Statistical analysis was performed on the raw data obtained from this study. With regards to the presence or absence of the Eclipse Sign, a sign of potential ACL-PCL impingement, a McNemar's test was used. For analyzing displacement of the femoral tunnels from the center of the native ACL footprints, a signed rank test was performed. All p-values were set to 0.05.

III. Results

Upon arthroscopic examination of the native femoral ACL insertion from the lateral viewing portal, all eight cadaver knees demonstrated no overlapping of the ACL footprint by the PCL as the knee was ranged from 0-120 degrees of flexion. Using the anteromedial portal technique, the femoral tunnel guide-wire was placed into the center of the native ACL footprint in all eight knees. When femoral tunnels were drilled anteromedially, there were no instances where the PCL obscured any portion of the tunnel as the knee was flexed from 0-120 degrees (Figure 4). Of the eight tunnels drilled trans-tibially, all had the femoral tunnel guide-wire within the broad ACL footprint; however, after the core reamer was used to drill a tunnel, three cases showed clear evidence of a femoral tunnel being obscured by the lateral border of the PCL during flexion of 90 to 120 degrees when viewed from the lateral arthroscopy portal ($p = 0.25$). We called this finding the "Femoral Eclipse Sign" (Figure 3). This implied that a graft placed in those three tunnels would experience impingement against the lateral border of the PCL during high flexion.

When measuring the direction and magnitude of displacement from the absolute center of the native ACL footprint, it was noted that all tunnels drilled using the anteromedial portal method had zero displacement. With regard to the trans-tibially drilled tunnels, the three tunnels that showed signs of potential PCL impingement (positive Eclipse Sign) were displaced superiorly (Figure 5). The amount of superior displacement was measured to be 2 mm, 5 mm, and 5 mm. Of the remaining five tunnels drilled trans-tibially that did not show potential PCL impingement (negative Eclipse Sign), all were displaced anteriorly, superiorly, or anterosuperiorly from the anatomic center of the ACL footprint (Table 1). Overall, the degree of displacement from the center of the native ACL footprint of trans-tibially drilled femoral tunnels averaged 3.25mm ($p = 0.0078$, range 1 to 5 mm).

IV. Discussion

This study compared the incidence of potential ACL-PCL impingement using the traditional trans-tibial femoral tunnel drilling method15 to a technique of independent drilling through the anteromedial arthros-

copy portal.20 In addition, the ability to place a femoral tunnel in the center of the native ACL footprint using these two drilling techniques was measured. Recent literature has demonstrated many benefits of placing an ACL graft in a more oblique and anatomic orientation centered in the native ACL footprint.1, 4, 8-11, 13 These advantages include avoiding graft impingement on the PCL and the resultant increased graft tension, loss of knee flexion, graft laxity and failure that may accompany it. It has become recognized that a vertically oriented graft can lead to ACL-PCL impingement, fatigue failure and rotatory instability.23-26 To prevent these potential complications, many have advocated drilling the femoral tunnel independently through an anteromedial portal.6, 20, 26 This technique has consistently led to an anatomically placed single bundle ACL without the risk of creating a short femoral tunnel with possible violation of the posterior femoral cortex.7, 19

In our study, native femoral ACL footprints and femoral tunnels drilled through an anteromedial portal did not show signs of potential PCL impingement. In addition, all eight tunnels drilled anteromedially were centered in the native ACL footprint. Three tunnels (37.5%) drilled trans-tibially showed obscuring of the tunnel by the PCL as the knee was brought into high flexion – a sign that a graft placed into the tunnel would likely press against the lateral border of the PCL. Overlapping of the femoral tunnel by the PCL was referred to as the "Femoral Eclipse Sign," and this intra-operative finding was seen as a useful tool to avoid ACL-PCL impingement. All tunnels that showed a positive Eclipse Sign were displaced superiorly by an average of 4 mm – evidence that the tunnels were too vertical. We concluded that because femoral tunnels drilled through an anteromedial portal were oriented more anatomically, they did not show signs of potential PCL impingement. The three tunnels that showed signs of PCL impingement were likely the result of the trajectory of the tibial tunnel compromising the orientation of the femoral tunnel. In addition, the remaining five (62.5%) tunnels drilled trans-tibially that did not show signs of impingement were displaced from the absolute center of the native ACL footprint (Table 1).

Limitations to this study include using a cadaver model and the fact that the sample size is small. In having to drill two tunnels in a human femur to compare the anteromedial portal versus trans-tibial technique, it was not feasible to perform this study in an in vivo model. Using a cadaver model was advantageous, providing a distinct visual illustration of the potential difference in the two methodologies. The small sample size may have lead to less precise findings, as the statistical significance of the Eclipse Sign was definitely impacted. Still, the correlation between the incidence of the Eclipse Sign and drilling technique definitely showed that it is a useful intra-operative tool to signal a vertical, PCL-impinging graft position. The current study has shown that the proposed anteromedial portal drilling technique has the potential to decrease ACL-PCL impingement during ACL reconstruction.

Another weakness is the fact that an ACL reconstruction was not carried out to validate the Femoral Eclipse Sign. Performing ACL reconstructions in our specimens would require drilling complete femoral tunnels. We elected to use core reamers to outline the positions of the tunnels, thus preserving bone stock and allowing full visualization of two tunnel positions relative to the center of the native ACL footprint within the same knee. We believe that validating the Eclipse Sign is a necessary step in solidifying the conclusion that anatomic tunnel placement, most consistently achieved by the anteromedial portal drilling method, leads to a lower incidence of ACL-PCL impingement. As a result, a future clinical trial evaluating the Eclipse Sign and its correlation with true ACL-PCL impingement during ACL-PCL reconstruction is being planned.

The results of this study lead us to believe that a femoral tunnel centered in the native ACL footprint will not experience ACL-PCL impingement. From our experience, this orientation was most consistently achieved by drilling the femoral tunnel through an anteromedial portal.3, 6 Although Howell and Kondo have suggested modifications to the trans-tibial method to achieve a more anatomic graft placement, in our study, we were not able to obtain consistently accurate placement of the femoral tunnel using that technique. Regardless of the drilling method chosen, we recommend routinely checking for ACL-PCL impingement prior to graft insertion by observing whether the PCL obscures the femoral tunnel during high flexion – an intra-operative marker called the Femoral Eclipse Sign.

V. Conclusion

ACL-PCL impingement following ACL reconstruction can lead to increased graft tension, inability to achieve full flexion and graft laxity due to repetitive stress. To avoid this phenomenon, the femoral tunnel should be placed anatomically in the center of the native ACL footprint. This is most consistently achieved by drilling the femoral tunnel through the anteromedial arthroscopy portal. Future clinical studies are necessary to validate the Femoral Eclipse Sign.

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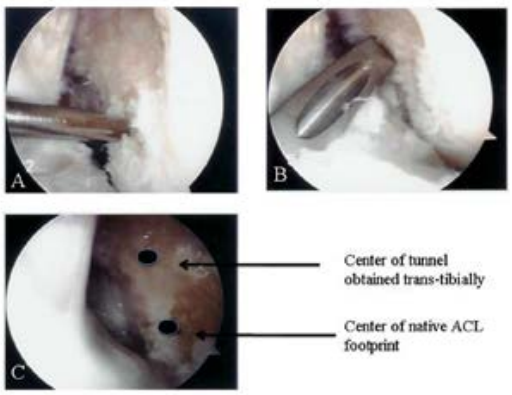

Fig. 1

a. Drill mark made in the center of the native ACL footprint.
b. Over-the-top guide inserted trans-tibially and an attempt made to place the tunnel in the center of the native ACL footprint.
c. Resulting superior displacement of the drill mark made trans-tibially relative to the center of the native ACL footprint.

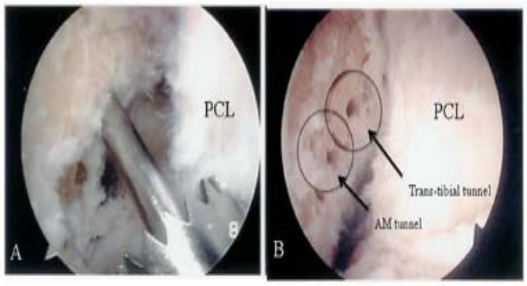

Fig. 2

a. Use of the core reamer allowed visualization of the femoral tunnel location while preserving bone stock – this allowed drilling of multiple tunnels in the same knee.
b. Illustration of the difference between the AM tunnel and the trans-tibial tunnel. Note the proximity of the trans-tibial tunnel to the PCL compared to the AM tunnel.

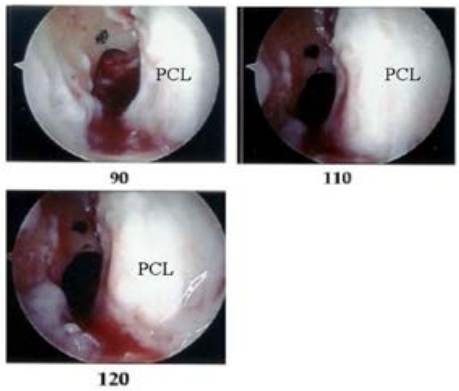

Fig. 3

The "Femoral Eclipse Sign." Tunnels drilled trans-tibially: as the knee is flexed from 90-120 degrees, the lateral border of the PCL obscures the medial aspect of the femoral tunnel. This is an intra-operative sign that any graft placed within this tunnel may potentially impinge against the PCL during knee flexion.

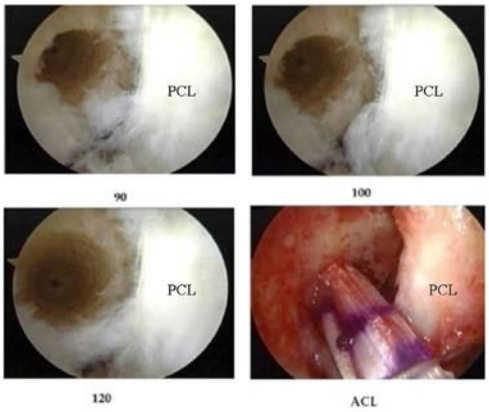

Fig. 4

Tunnels drilled through the anteromedial portal. No Eclipsing of the femoral tunnel is seen. The resulting graft does not impinge against the lateral border of the PCL at full flexion.

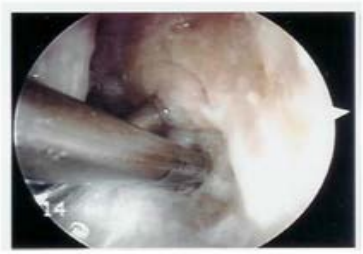

Fig. 5

The superior placement of the tunnel drilled trans-tibially compared to the tunnel drilled through the medial portal is illustrated here.

Table 1 : Three out of eight femoral tunnels drilled trans-tibially Eclipsed. All were positioned superior to the tunnel drilled though the medial portal

Data Set 1 : Presence of eclipse sign in femoral tunnels drilled through an anteromedial arthroscopy portal versus tunnels drilled trans-tibially

Knee	Native femoral ACL attachment	Tunnel drilled through anteromedial portal	Tunnel drilled trans-tibially
1	No eclipse	No eclipse	No eclipse
2	No eclipse	No eclipse	**Eclipse**
3	No eclipse	No eclipse	No eclipse
4	No eclipse	No eclipse	No eclipse
5	No eclipse	No eclipse	**Eclipse**
6	No eclipse	No eclipse	No eclipse
7	No eclipse	No eclipse	**Eclipse**
8	No eclipse	No eclipse	No eclipse

*0/8 femoral tunnels drilled through an anteromedial arthroscopic portal showed an Eclipse Sign – no sign of potential ACL-PCL impingement
**3/8 (37.5%) tunnels drilled trans-tibially showed an Eclipse Sign – thus there is a 37.5% chance of ACL-PCL impingement using the trans-tibial method

Data Set 2 : Amount and direction of displacement of femoral tunnels in relation to the native anatomic ACL footprint

Knee	Amount and direction of displacement: Anteromedial	Amount and direction of displacement: Trans-tibial
1	0mm	1mm anterior
2	0mm	5mm superior
3	0mm	4mm anterosuperior
4	0mm	1mm anterior
5	0mm	2mm superior
6	0mm	5mm anterosuperior
7	0mm	5mm superior
8	0mm	3mm anterosuperior

*All femoral tunnels drilled through an anteromedial portal were placed in the center of the native ACL footprint
*Femoral tunnels drilled trans-tibially were an average of 3.25mm displaced anterosuperior to the native ACL footprint

Global Journal of Medical Research: H
Orthopedic and Musculoskeletal System
Volume 14 Issue 1 Version 1.0 Year 2014
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals Inc. (USA)
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Plantar Dislocation of the First Metatarsophalangeal Joint

By Said Zizah, Amine Mezzani, Seringue Saliou, Kamal Lahrach, Amine Marzouki & Fawzi Boutayeb

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Abstract- Plantar dislocation of the first metatarsophalangeal joint is an extremely rare primary hyperflexion injury of forefoot. A 32-year-old female was admitted to our emergency with a deformity and pain on his right foot. Dislocation was caused by motor vehicle. On physical examination mild swelling of the first MTPJ and plantar dislocation of the great toe were evident. Diagnosis was made on anteroposterior, and medial oblique radiographs. They confirmed a plantar dislocation of the right first MTPJ. The patient was treated with closed reduction of the first metatarsophalangeal joint by means of distraction. Twenty months after surgery no osteoarthritic changes, no narrowing and no limitation of the first MTPJ were encountered. The clinical result was good and the patient was satisfied.

Keywords: *great toe, metatarsophalangeal joint, plantar dislocation.*

GJMR-H Classification: *NLMC Code: WE 304, WE 31*

Strictly as per the compliance and regulations of:

Plantar Dislocation of the First Metatarsophalangeal Joint

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Abstract- **Plantar dislocation of the first metatarsophalangeal joint is an extremely rare primary hyperflexion injury of forefoot. A 32-year-old female was admitted to our emergency with a deformity and pain on his right foot. Dislocation was caused by motor vehicle. On physical examination mild swelling of the first MTPJ and plantar dislocation of the great toe were evident. Diagnosis was made on anteroposterior, and medial oblique radiographs. They confirmed a plantar dislocation of the right first MTPJ. The patient was treated with closed reduction of the first metatarsophalangeal joint by means of distraction. Twenty months after surgery no osteoarthritic changes, no narrowing and no limitation of the first MTPJ were encountered. The clinical result was good and the patient was satisfied.**

Keywords: great toe, metatarsophalangeal joint, plantar dislocation.

I. Introduction

Dislocation of the first metatarsophalangeal joint is an uncommon injury. The anatomical complexity of the first metatarsophalangeal joint makes this injury one of a kind. Jahss [1] describes two cases in 25,000 patients (incidence of 0.008%) and Giannikas *et al.* [2] report four cases in 10,000 patients (incidence of 0.04%). The most common cause of this injury is a motor vehicle accident. Falls from heights and athletic injuries are secondary causes [1]. Most of these dislocations had been treated conservatively. We are reporting a case of isolated closed plantar dislocation of the first metatarsophalangeal joint after a classic severe primary hyperflexion injury of forefoot in a non-lactating female with no pre-existent deformities or muscular imbalances.

II. Patient and Observation

A 32-year-old female with no significant past medical history presented to the our Emergency Department with a chief complaint of a deformed and painful left first MPJ. The forefoot struck against the pedal of the motor vehicle while the body was projecting forward. Examination of the great toe revealed swelling and deformity with total functional impairment of the toe. There was no superficial laceration of the skin or neurovascular deficit. The first metatarsophalangeal joint was swollen and the axis of the great toe was altered to hyperextension. The blood supply and sensation to the great toe were intact. The other toes had normal sensation and capillary refill. Anteroposterior and medial oblique radiographs (Fig. 1a and b) revealed the plantar dislocation of the first metatarsophalangeal joint without associated fracture (Figure 4). The tibial and fibular sesamoids were found in relatively correct anatomic position to the first metatarsal head and to one another. There were no fractures visualized on any of the views of the left foot.

Immediate closed reduction of the metatarsophalangeal joint was performed under local anaesthesia and it was successful. The proximal phalanx was grasped and hyperextended onto the dorsal aspect of the first metatarsal with strong distraction. This resulted in a relocation of the first MPJ. After reduction, the stability and the range of movement (ROM) were checked and found to be satisfactory. The length of the first ray also appeared to be restored. For additional stability, fixation of the MTP joint was performed with a below knee cast was applied. The cast were removed after four weeks and weight bearing exercises started. The patient was prescribed a regimen of physical therapy that included ultrasound, whirlpool, stretching, and strengthening exercises for the first MPJ. Her activity status was weight bearing as tolerated, with progression to normal shoe gear over the next 4 months. One year after injury, the patient was asymptomatic and had full ROM of the MTP joint. At the clinical evaluation there was no deformity of the forefoot. The patient walked without pain and performed sports activities.

III. Discussion

The plantar dislocation is an extremely rare historical event [3, 4, 1, 5]. The anatomical structures of the joint, the direction and mechanics of the trauma and the type of shoe worn at the moment of the trauma all affect the type of the first MTPJ dislocation which can occur [4, 6, 7].

As the dorsal dislocation is produced by hyperextension injury of the forefoot [1], 2, 3, 8, 9], hyperflexion injury of the forefoot is incriminated as the primary mechanism in plantar dislocation of the metatarsophalangeal joint [3, 6, 9].

Garcia Mata et al. [10] reported a case of plantar dislocation of the first metatarsophalangeal joint in a lactating lady following minor trauma and noted the

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presence of physiological ligamentous laxity associated with normal increase in progesterone in lactating ladies. In 1988, Biyani et al. [6] reported a case of severe open plantar pan-metatarsophalangeal joint dislocation. The mechanism of injury, which they described, was a severe hyperflexion injury following a fall from 20 feet height. We report an example of a complete dislocation of the first MTPJ which occurred in a young woman. To our knowledge, this is the fourth case in literature which was treated by closed reduction of the plantar dislocation of the MTPJ of the great toe.

The plantar dislocation of the first metatarsophalangeal joint by Prasad et al. [11] constitute high energy injuries, resulting from fall from heights and represent Grade V of kodali's [12] modification of the classification by Clanton et al. [13]. They noted asymptomatic hallux valgus later and drew attention to the inherent difficulty in the identification of potential instability even after diligent intra-operative assessment. They pointed out that neither the mechanism nor the resultant injury is representative of plantar dislocation because of the pre-existent foot drop and can only be construed as a pathological injury.

Radiographs are very useful for detecting the relationship between the heads of the joints and for excluding fractures. In cases of dislocation of the first metatarsophalangeal joint, radiographs can show signs of chronic pathology (e.g., hallux rigidus). However, there is no agreement about the study of the controlateral foot using radiographs [14]. Some authors report that sequential radiographs could be very useful for diagnosing the proximal loosening of the sesamoids [14].

Once the diagnosis is certain, the dislocation should be reduced as soon as possible. Immediate reduction of the dislocation can limit numerous complications (e.g. ecchymosis, swelling, vascular compromise of the skin, etc.). After the closed reduction of the first metatarsophalangeal, a clinical examination of joint stability is necessary. This will enable evaluation of the integrity of the ligaments (varus-valgus stress, plantar and dorsal draw) and muscular strength.

A surgical approach is only used if a closed reduction is impossible [1, 8, 15]. There are various causes for the failure of closed reduction. It can be blocked by entrapment of the metatarsal head through the 'buttonhole' of the capsule [8]. Time between injury and intervention is a factor which influences the ability to obtain closed reduction [1]. After closed or open reduction, some authors recommend percutaneous fixation with Kirschner wire in cases in which the joint is unstable [15].

Follow-up of these injuries has showed good results with very less morbidity. In the literature, in association with dislocations of MP joints, skeletal injuries are also reported: avulsion fractures of the sesamoid, fractures of proximal phalanges and metatarsal fractures. Obviously, in these cases, the result can be different according to the severity of the fractures.

IV. Conclusion

Provided the patient presents soon after injury, closed reduction is easily performed. Proper evaluation of the clinical and radiographic evidence is essential to classify the type of MTP dislocation, which is helpful in deciding the type of reduction method required to treat this rare injury. Concomitant injuries should also be looked for while treating this injury which may aid in closed reduction.

Cmpeting interests: The authors declare no competing interest.

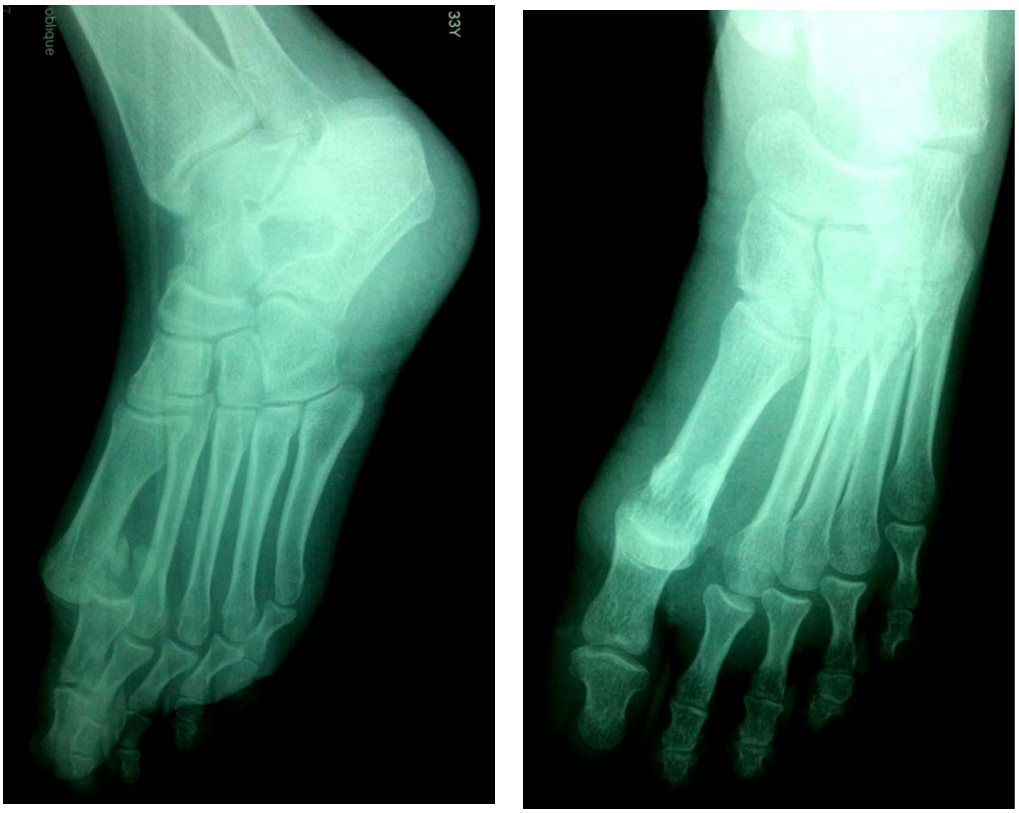

Figure 1 : Radiographs of planto-lateral dislocation of the first metatarsophalangeal joint.

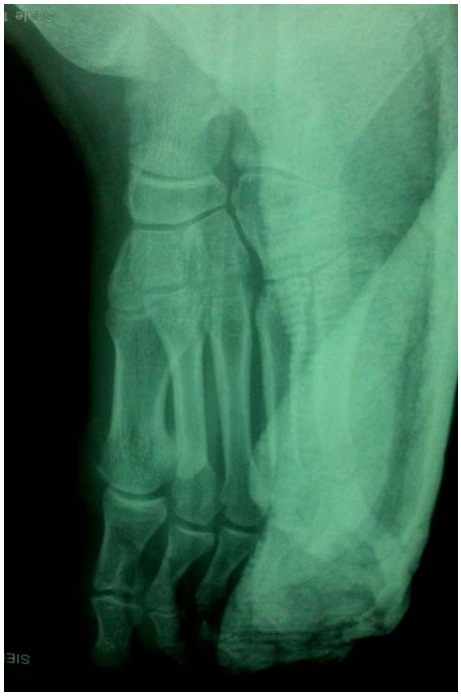

Figure 2 : Radiograph after initial reduction of the first metatarsophalangeal dislocation

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Global Journal of Medical Research: H
Orthopedic and Musculoskeletal System
Volume 14 Issue 1 Version 1.0 Year 2014
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals Inc. (USA)
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Comparison of Outcomes and Complications Acetabular Reconstruction using an Antiprotrusio Cage and a Cemented Dual Mobility Cup or Simple Polyethylene Cup

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Abstract- The current study evaluated the outcome of a retrospective series of 37 revision total hip arthroplasties with severe acetabular bone defects reconstruction using an antiprotrusio cage. We aimed to compare the peri and postoperative complications and mid-term outcomes of two groups, a reconstruction using a dual mobility cup (DMC) cemented into the cage (n=14) or a cemented simple polyethylene cup (SPEC) (n=23) at a mean follow-up of 5 years. We found an inverse association between the use of DMCs and both dislocation rate ($p<0.05$) and dislocation undergoing revision ($p<0.05$). No aseptic loosening was found in the DMC-group and there were no differences in the rest of the complications between the DMC-group and the SPEC-group ($p>0.05$). In conclusion, DMCs demonstrated excellent results at mid-term follow-up in terms of prevention of instability and stable cemented fixation.

Keywords: total hip arthroplasty, revision total hip arthroplasty, hip instability, hip dislocation, dual mobility cup, reinforcement cage device.

GJMR-H Classification: NLMC Code: WE 312

Strictly as per the compliance and regulations of:

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Abstract- The current study evaluated the outcome of a retrospective series of 37 revision total hip arthroplasties with severe acetabular bone defects reconstruction using an antiprotrusio cage. We aimed to compare the peri and postoperative complications and mid-term outcomes of two groups, a reconstruction using a dual mobility cup (DMC) cemented into the cage (n=14) or a cemented simple polyethylene cup (SPEC) (n=23) at a mean follow-up of 5 years. We found an inverse association between the use of DMCs and both dislocation rate ($p<0.05$) and dislocation undergoing revision ($p<0.05$). No aseptic loosening was found in the DMC-group and there were no differences in the rest of the complications between the DMC-group and the SPEC-group ($p>0.05$). In conclusion, DMCs demonstrated excellent results at mid-term follow-up in terms of prevention of instability and stable cemented fixation.

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I. Introduction

The demand for primary total hip arthroplasty (THA) is expected to increase over the next several decades, due to the increased life expectancy of THA patients and a trend towards surgical indication at younger ages [1]. Demand for THA revisions is projected to double by 2026, and case complexity is likely to increase dramatically [1]. Despite surgical technique and implant design improvements, instability remains the leading cause of mechanical failure of revision THAs accounting for up to 35% of these failures [3]. Different salvage procedures have been proposed in an attempt at stabilizing the hip. The most common option for treating recurrent dislocation in the United States is revision with a constrained acetabular component [14]. Constrained designs have reduced postoperative dislocation rates, but only to a limited extent and to the detriment of long-term acetabular fixation [2]. Dual mobility cups (DMCs) were introduced to prevent instability following THA, particularly in patients at high risk for dislocation, with fewer mechanical complications and lower loosening rates than with constrained acetabular components [1,3].

The advantages of acetabular revisions with antiprotrusio cages and the value of DMCs separately in terms of quality of fixation and prevention of instability were evaluated in our study. We did a retrospective series comparing functional and radiographic outcomes and complications of two groups, one with a simple polyethylene cup (SPEC) and other with a cemented DMC. We analyzed possible risk factors of dislocations, such as age, sex, number of previous surgeries, approach route, the size of the cages and cups and preoperative bone loss.

II. Material and Methods

A retrospective single-center study was performed between January 2003 and December 2011. All patients undergoing acetabular revision using antiprotrusio cage and cemented DMCs and SPECs were included; unipolar femoral revisions or revisions THA for tumor were excluded.

This study included 37 patients: 25 females and 12 males, with an average age at revision of 67.8 years (range, 29 —90 years). 17 left and 20 were right hips. Osteoarthritis was the most common cause of THA (Fig.1).

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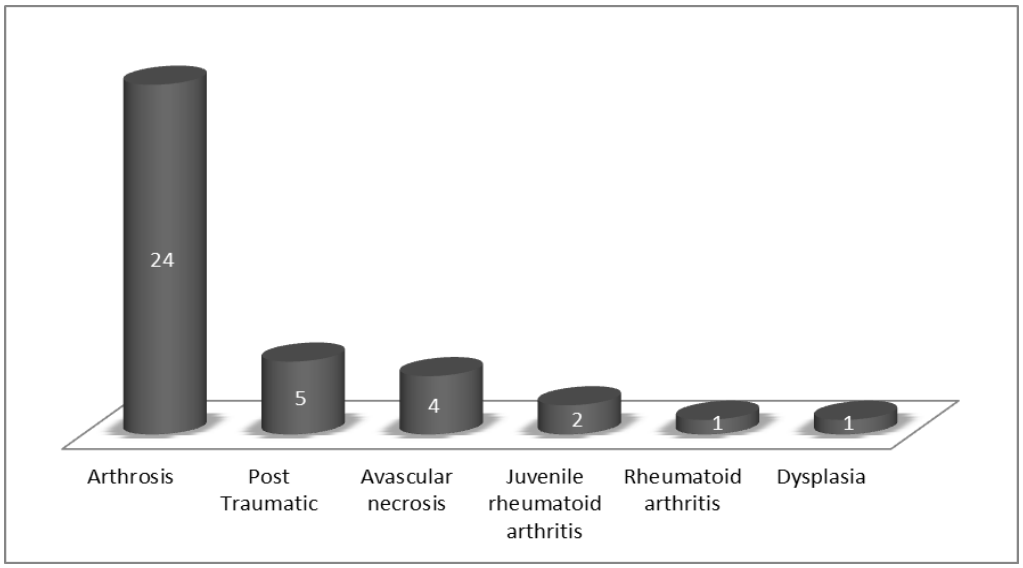


Figure 1 : Indications that led to primary hip arthroplasty

The average time from index arthroplasty to the acetabular revision was 13.4 years (range, 1- 27 years). We revised 25 hips for aseptic loosening, 3 for acetabular fracture and eight for recurrent dislocation associated to acetabular loosening. One hip had been previous infected although at the time of the index surgery the infection was controlled. The time from the last procedure to acetabular revision was 7.4 years (range, 0.2- 27 years). The number of previous surgeries on the hip in question averaged 1.9 and was: 1 (16), 2 (12), 3 (5), 4 (3), and 5 (1).

A postero-lateral approach was used in 32 cases (87%), in one case with femoral trochanteric osteotomy. A Hardinge transgluteal approach was used in 3 cases (8%), and Smith-Petersen anterior approach in two cases (5%). The hip joint was exposed and the acetabular component was removed and the femoral component was tested. Once the acetabulum had been cleaned, the severity of the acetabular defect was graded using the Paprosky classification system [4]: 2b (12), 2c (8), 3a (8) y 3b (9). Bone defects were filled with bone graft, using in two cases structural graft. Of the 37 cages used in this study, 15 performed initially were of the Protrusio cage [DePuyOrthopaedics, Inc, Warsaw, IN], and the latter 22 Contour types [Smith and Nephew Richards, Memphis, TN]. We used on average 6.6 screws (range, 3-9 screws) to secure the reconstruction cages. We cemented a SPEC into the cage in 23 hips. In 14 hips the device used was a DMC, Polar Cup [Smith and Nephew Richards, Memphis, TN]. The femoral component also was revised in 9 of the 37 cases. Postoperatively, patients were treated with protected weightbearing for 6 to 12 weeks and then were allowed to progress to full weightbearing as tolerated.

The Postel Merle d'Aubigné (PMA) score [5] was used to assess patient function. The radiological assessment was performed on an A/P view of the pelvis and A/P and lateral views of the hip. For the cups, radiolucency, osteolysis and cavities were identified and located by DeLee and Charnley zones [6]. The position of the centre of rotation was compared to the ''optimal'' centre of rotation defined by Ranawat et al [7]. The outcome of grafting was evaluated seeing incorporation, resorption or fracture of the bone graft [8]. Clinical failure of the acetabular reconstruction was defined as occurrence of instability and radiographic failure was defined as a failure of the antiprotrusio cage, like breakage of the material [3], and/or definite loosening of the cemented insert and/or resorption of the allograft.

We compare outcomes, complications and revision rates between the DMC-group and SPEC-group. We recorded all dislocation episodes, obtaining the incidence of implant dislocations at the end of follow-up (FU). We analyzed possible risk factors of dislocations, such as age, sex, number of previous surgeries, approach route, size of cages and cups and preoperative bone loss.

The statistical tests, carried out using STATA tm/SE v10, included univariate parametric tests with a critical p value less than 0.05.

III. Results

FU averaged 5.4 years; the longest FU was 12.5 years. Preoperative PMA functional scores [5] averaged 5.48 ± 2.41. We observed an improvement ($p < 0.01$) in the postoperative score with an average PMA of 10.55 ± 3.82. Every component of the PMA changed significantly ($p < 0.001$). There were no significant differences between DMC-group and SPEC-group, with a mean PMA score 10.4±3.8 and 10.4±3.7 ($p>0.05$) (Fig.2).

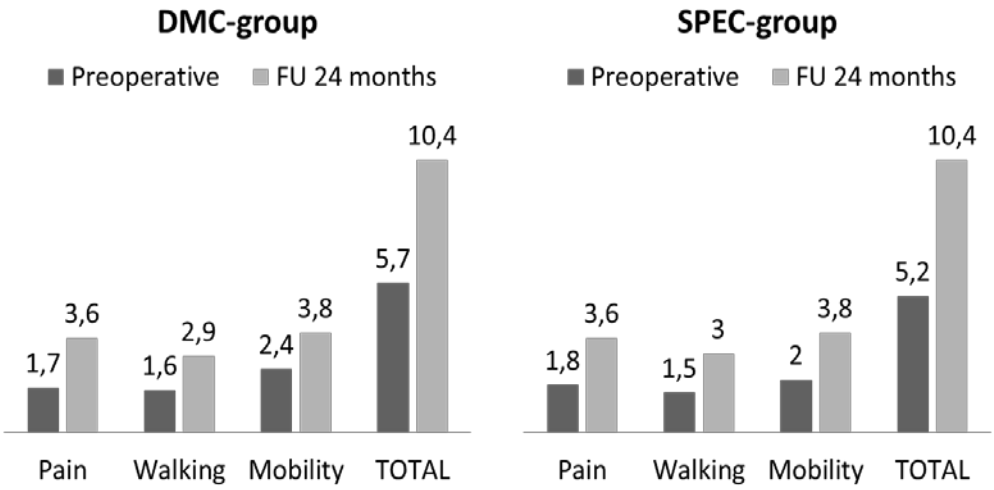


Figure 2 : Change in the Postel Merle dÁubigné from preoperative to follow-up in DMC-group compared with SPEC-group

Perioperative complications comprised: 1 greater trochanter fracture managed by plate fixation, 1 superficial infection resolved with antibiotic treatment and 5 inmediate postoperative sciatic nerve palsies with full functional recovery.

As postoperative complications we found (Table1): four deep infections (10.8%), one early infection requiring surgical lavage, which resolved the infetcion and three septic acetabular loosening (8.1%). One was associated to recurrent dislocations and a fracture of the superior flange of the cage, a revision was necessary at 44 months postoperatively using a constrained liner cemented into a new reconstruction cage. Another was revised at 36 months, and the last one refused to have surgery.

Three aseptic cage loosenings, of which only one was revised at 84 months. In this case a Protrusio cage lost fixation and impinged the sciatic nerve, so a revision to another cage and neurolysis of the sciatic nerve was necessary.

A cemented DMC lost fixation (7.1%) at 24 months, which was revised, leaving the cage intact, with no further complications.

We observed two material ruptures (screw or cage) (5.4%): the above-mentioned septic loosening with a Contour superior flange fracture and an ischial screw fracture that moved and impinged the sciatic nerve requiring the prompt removal of the screw, leaving the cage intact.

Three cases of late sciatic nerve palsies, which needed revision, explained aboved. There was a fracture of the ischium 12 months later with posterior fibrosis of the sciatic nerve that need neurolysis.

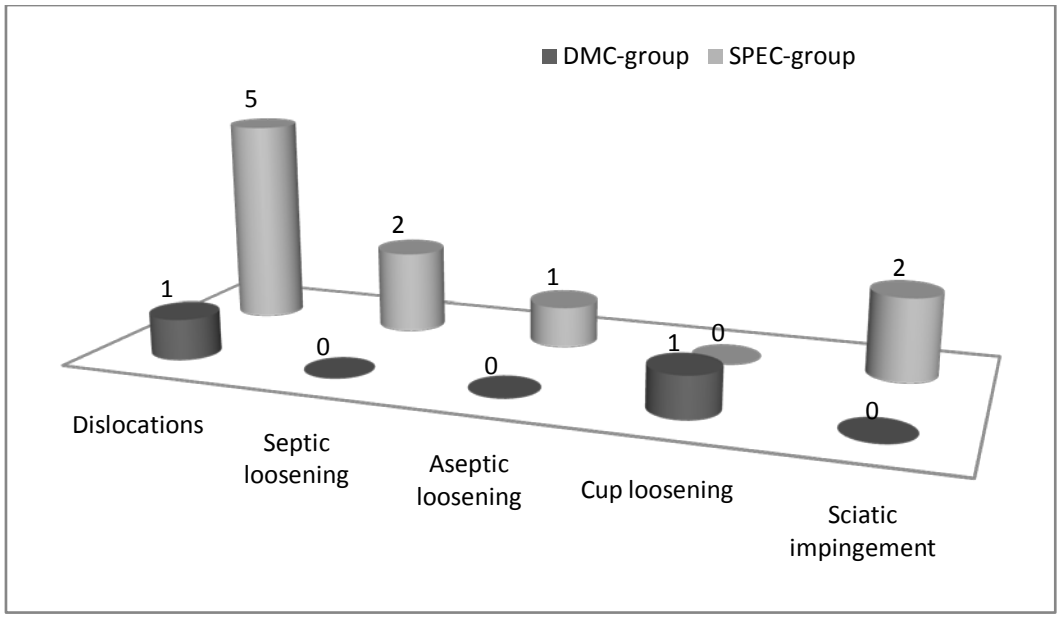
The overall postoperative dislocation rate at end of FU was 27% (10 dislocations). There were 3 cases of early dislocations that were reduced without additional surgery and remained recurrence-free. Seven hips (18.9%) needed further revision. One case was associated with septic loosening as explained above. Another two cases were revised to DMCs, without further complications. In two patients aged 89 and 90 respectively a resection arthroplasty was left. One of them died of causes unrelated to the process 24 months after the surgery. Another one was revised to a SPEC and dislocated two times again, Then another revision was needed to a DMC, without recurrence. The last patient was a dislocation of the femoral head from the mobile polyethylene (PE) component inside the metal shell, a so-called intraprosthetic dislocation, 3 months postoper-atively, being this the only case of DMC dislocation. After several attempts of closed reduction, an open reduction and revision to a constrained liner was necessary (Table 1). In summary, two constrained liners were used because of recurrent dislocations.

Table 1 : Complications occurred in DMC-group and SPEC-group

Complications	SPEC-group (n=23)	DMC group (n=14)	Chi² test
Infection	3 (3 septic loosening)	1	p>0.05
Aseptic loosening	2	1	p>0.05
Cup loosening	0	1	p>0.05
Material ruptures	2	0	p>0.05
Dislocations	9	1	p<0.05
Clinical and radiographic failure	10	3	p<0.05
Revision for any reason	10	2	p<0.05

We found an inverse association between the use of DMCs and both dislocation rate ($p<0.05$) and dislocation undergoing revision ($p<0.05$). We also found that a lower dislocation rate was found in patients with a lower age ($p < 0.005$). None of the other predefined risk factors significantly affected dislocation rates in the present series (Table 1). The need for reoperation for any reason was 32%, twelve hips (Table1) (Fig.3).

Figure 3 : Need for reoperation for any reason in SPEC-group and DMC-group



Thirty-four (92%) structural allografts and morselized cancellous grafts healed uneventfully without fracture or resorption. All acetabular reconstructions (100%) presented no radiolucent line around the cemented SPEC and 1 DMC (7%) presented radiolucent lines around the cemented insert that ended in a cup loosening and the need of revision. After the revision, a theoretically ''optimal'' centre of rotation (<10 mm) [7] was found in 20 cases (54%), 10-20mm in 14 cases (38%) and > 20 mm in 3 cases (8%). The mean vertical and lateral displacement of the centre of rotation was similar for DMC-group and SPEC-group. Reconstruction using an antiprotrusio cage associated with a DMC made it possible to obtain a mean cup inclination of 46◦ ±4.46◦, similar to the SPEC with a cup inclination of 49◦ ±5.80◦ ($p>0.05$).

IV. Discussion

Combining technical difficulties related not only to the reconstruction of severe bone defects and the fixation of the acetabular component but also to a high risk of instability, revision THA remains a challenge particularly in the cases of Paprosky grade II and III [3].

The presence of severe bone loss is an indication for an acetabular reconstruction with the use of a metal reinforcement ring and bone graft. The use of a reinforcement device and bone grafting increases the success rate because it protects from excessive forces while providing support of the cup, approximation of the normal anatomy, restoration of lower-limb length, and better bone stock in case of future revision [9]. However, this technique is highly demanding and requires a wide exposure of the ischium and retraction of the soft tissue to place the inferior flange, which is associated with higher risk of sciatic nerve injury [10]. We reported 5 cases of sciatic nerve palsies that occurred in the perioperative period (14%), confirming the high risk of sciatic nerve palsy.

In addition, rates of instability as high as 25% have been reported, mainly due to the large dissection required to insert this implant [3], but also because of high number of previous surgeries and poor abductor function [10]. Constrained implants have been recommended by some authors where the risk of postoperative dislocation is high [1]. However, the success of the constrained design must be balanced against the theoretical possibility of increased transmission of stress to the implant-bone or implant-cement interface leading to loosening because of decreased ROM and early impingement [11]. It therefore seems logical to suggest caution in the use of these constraining devices [11].

In the recent days, DMCs have grown as an effective device in the treatment and prevention of instability following THA, particularly in patients at high risk for dislocation, with fewer mechanical complications

and lower loosening rates than with constrained acetabular components [1, 3, 11-15]. The overall survival rate of DMCs has been reported to be as high as 96% at 15-year follow-up with a restoration of hip stability in more than 95% of operated patients [2, 11-13]. This might be related to the fact that with a DMC, most of the motion occurs within the inner bearing patients [11] avoiding overstressing the cement-metal and the bone-cement interfaces.

The current series compared the use of an acetabular reconstruction technique using an antiprotrusio cage, on the one hand, with a DMC cemented into the cage and, on the other hand, a SPEC. At a mean FU of 5 years, no failure of the acetabular reconstruction was observed in 56.6% of the patients in the SPEC-group and in 78.6% of the patients in the DMC-group ($p<0.05$). Results that are similar to those obtained by Wegrzyn et al, with no failure of the acetabular reconstruction in 98% of the patients at mean FU of 7.5 years [3], or by Langlais et al, with no failure in 94.6% of 88 cemented DMCs [15].

A concern for long-term fixation of cemented DMCs is the poor results observed with cemented metal cups and with cemented metal-backed polyethylene cups [15].We reported one case (7.1%) of dissociation of cemented DMC and no cases of dissociation of SPECs. Recent studies demonstrated that cementation of DMCs provided even greater fixation strength than SPEC [1].

We reported a 39% dislocation rate (9/23) during the analysis of 23 reconstruction cages using a SPEC. Displaying the high rate of dislocations obtained using these devices, we began using a DMC cemented into the cage, improving our rates of 39% to 7.1% (1/14). We saw that using a cemented DMC into the cage, dislocation rate and dislocation undergoing revision dropped ($p=0.03$). Furthermore, the only case of DMC dislocation that we observed was a dislocation of the femoral head from the mobile polyethylene component inside the metal shell, a so-called intraprosthetic dislocation. Guyen et al reported two cases of intraprosthetic dislocation at the inner bearing [12]. They ensured that this was typically a medium- to long-term complication of DMC. Cold-flow failure and wear of the capturing area of the polyethylene component related to impingement of the prosthetic femoral neck against the chamfer are responsible for this complication [12]. The use of a femoral component with a thin Morse taper (10/12 Morse taper) and a highly polished neck to reduce abrasive wear is recommended to prevent this complication [12]. Our results are similar to those obtained By Schneider et al, at a mean FU of 41 months with 10.4% dislocation rate and without intraprosthetic dislocations of 96 cemented DMCs [16]. Wegrzyn et al reported no instability [1] and Langlais et al obtained a low dislocation rate of 1.1% of 88 cemented DMCs [15].

We analyzed possible risk factors of dislocations, obtaining that a lower dislocation rate was found in patients with a lower age ($p < 0.005$). None of the other predefined risk factors significantly affected dislocation rates in the present series. Therefore we could assign lower age at revision as a positive predictive value for postoperative dislocation. Langlais et al ensured that for patients older than 70 years of age, the risk of dislocation increases twofold [15].

We obtained a mean cup inclination of 46◦ ±4.46◦ (DMCs), similar to the SPECs with a cup inclination of 49◦ ±5.80◦ ($p>0.05$). The anatomical centre of rotation [7] was obtained in 8 cases in the DMC-group and in 12 cases in the other. Placing the acetabular component at the correct anatomical position decreases the risk of acetabular component loosening [1] and the risk of impingement and dislocation [1].

Our study had significant limitations. First, it was a retrospective study. Second, two reconstruction devices were used in the patients and may have confused the results. Third, midterm follow-up limited our ability to generate definitive conclusions with a power analysis, especially in relation to cup loosening. Finally, there were only 37, so larger studies with longer follow-up periods are needed.

Although a longer follow-up is required before reaching definitive conclusions, our preliminary results indicate that the treatment of severe acetabular defects by DMCs cemented into antiprotrusio cages is a viable option as they prevent instability. DMCs do not seem to have a negative impact on acetabular fixation.

V. Acknowledgements

Our thanks are due to Mr. Martin J. Smyth, B.A., for his help in revising the English.

VI. Conflict of Interest

The authors declare that they have no conflicts of interest concerning this article.

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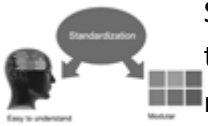

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4. Manuscript's Category,

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Before start writing a good quality Computer Science Research Paper, let us first understand what is Computer Science Research Paper? So, Computer Science Research Paper is the paper which is written by professionals or scientists who are associated to Computer Science and Information Technology, or doing research study in these areas. If you are novel to this field then you can consult about this field from your supervisor or guide.

TECHNIQUES FOR WRITING A GOOD QUALITY RESEARCH PAPER:

1. Choosing the topic: In most cases, the topic is searched by the interest of author but it can be also suggested by the guides. You can have several topics and then you can judge that in which topic or subject you are finding yourself most comfortable. This can be done by asking several questions to yourself, like Will I be able to carry our search in this area? Will I find all necessary recourses to accomplish the search? Will I be able to find all information in this field area? If the answer of these types of questions will be "Yes" then you can choose that topic. In most of the cases, you may have to conduct the surveys and have to visit several places because this field is related to Computer Science and Information Technology. Also, you may have to do a lot of work to find all rise and falls regarding the various data of that subject. Sometimes, detailed information plays a vital role, instead of short information.

2. Evaluators are human: First thing to remember that evaluators are also human being. They are not only meant for rejecting a paper. They are here to evaluate your paper. So, present your Best.

3. Think Like Evaluators: If you are in a confusion or getting demotivated that your paper will be accepted by evaluators or not, then think and try to evaluate your paper like an Evaluator. Try to understand that what an evaluator wants in your research paper and automatically you will have your answer.

4. Make blueprints of paper: The outline is the plan or framework that will help you to arrange your thoughts. It will make your paper logical. But remember that all points of your outline must be related to the topic you have chosen.

5. Ask your Guides: If you are having any difficulty in your research, then do not hesitate to share your difficulty to your guide (if you have any). They will surely help you out and resolve your doubts. If you can't clarify what exactly you require for your work then ask the supervisor to help you with the alternative. He might also provide you the list of essential readings.

6. Use of computer is recommended: As you are doing research in the field of Computer Science, then this point is quite obvious.

7. Use right software: Always use good quality software packages. If you are not capable to judge good software then you can lose quality of your paper unknowingly. There are various software programs available to help you, which you can get through Internet.

8. Use the Internet for help: An excellent start for your paper can be by using the Google. It is an excellent search engine, where you can have your doubts resolved. You may also read some answers for the frequent question how to write my research paper or find model research paper. From the internet library you can download books. If you have all required books make important reading selecting and analyzing the specified information. Then put together research paper sketch out.

9. Use and get big pictures: Always use encyclopedias, Wikipedia to get pictures so that you can go into the depth.

10. Bookmarks are useful: When you read any book or magazine, you generally use bookmarks, right! It is a good habit, which helps to not to lose your continuity. You should always use bookmarks while searching on Internet also, which will make your search easier.

11. Revise what you wrote: When you write anything, always read it, summarize it and then finalize it.

12. Make all efforts: Make all efforts to mention what you are going to write in your paper. That means always have a good start. Try to mention everything in introduction, that what is the need of a particular research paper. Polish your work by good skill of writing and always give an evaluator, what he wants.

13. Have backups: When you are going to do any important thing like making research paper, you should always have backup copies of it either in your computer or in paper. This will help you to not to lose any of your important.

14. Produce good diagrams of your own: Always try to include good charts or diagrams in your paper to improve quality. Using several and unnecessary diagrams will degrade the quality of your paper by creating "hotchpotch." So always, try to make and include those diagrams, which are made by your own to improve readability and understandability of your paper.

15. Use of direct quotes: When you do research relevant to literature, history or current affairs then use of quotes become essential but if study is relevant to science then use of quotes is not preferable.

16. Use proper verb tense: Use proper verb tenses in your paper. Use past tense, to present those events that happened. Use present tense to indicate events that are going on. Use future tense to indicate future happening events. Use of improper and wrong tenses will confuse the evaluator. Avoid the sentences that are incomplete.

17. Never use online paper: If you are getting any paper on Internet, then never use it as your research paper because it might be possible that evaluator has already seen it or maybe it is outdated version.

18. Pick a good study spot: To do your research studies always try to pick a spot, which is quiet. Every spot is not for studies. Spot that suits you choose it and proceed further.

19. Know what you know: Always try to know, what you know by making objectives. Else, you will be confused and cannot achieve your target.

20. Use good quality grammar: Always use a good quality grammar and use words that will throw positive impact on evaluator. Use of good quality grammar does not mean to use tough words, that for each word the evaluator has to go through dictionary. Do not start sentence with a conjunction. Do not fragment sentences. Eliminate one-word sentences. Ignore passive voice. Do not ever use a big word when a diminutive one would suffice. Verbs have to be in agreement with their subjects. Prepositions are not expressions to finish sentences with. It is incorrect to ever divide an infinitive. Avoid clichés like the disease. Also, always shun irritating alliteration. Use language that is simple and straight forward. put together a neat summary.

21. Arrangement of information: Each section of the main body should start with an opening sentence and there should be a changeover at the end of the section. Give only valid and powerful arguments to your topic. You may also maintain your arguments with records.

22. Never start in last minute: Always start at right time and give enough time to research work. Leaving everything to the last minute will degrade your paper and spoil your work.

23. Multitasking in research is not good: Doing several things at the same time proves bad habit in case of research activity. Research is an area, where everything has a particular time slot. Divide your research work in parts and do particular part in particular time slot.

24. Never copy others' work: Never copy others' work and give it your name because if evaluator has seen it anywhere you will be in trouble.

25. Take proper rest and food: No matter how many hours you spend for your research activity, if you are not taking care of your health then all your efforts will be in vain. For a quality research, study is must, and this can be done by taking proper rest and food.

26. Go for seminars: Attend seminars if the topic is relevant to your research area. Utilize all your resources.

27. Refresh your mind after intervals: Try to give rest to your mind by listening to soft music or by sleeping in intervals. This will also improve your memory.

28. Make colleagues: Always try to make colleagues. No matter how sharper or intelligent you are, if you make colleagues you can have several ideas, which will be helpful for your research.

29. Think technically: Always think technically. If anything happens, then search its reasons, its benefits, and demerits.

30. Think and then print: When you will go to print your paper, notice that tables are not be split, headings are not detached from their descriptions, and page sequence is maintained.

31. Adding unnecessary information: Do not add unnecessary information, like, I have used MS Excel to draw graph. Do not add irrelevant and inappropriate material. These all will create superfluous. Foreign terminology and phrases are not apropos. One should NEVER take a broad view. Analogy in script is like feathers on a snake. Not at all use a large word when a very small one would be sufficient. Use words properly, regardless of how others use them. Remove quotations. Puns are for kids, not grunt readers. Amplification is a billion times of inferior quality than sarcasm.

32. Never oversimplify everything: To add material in your research paper, never go for oversimplification. This will definitely irritate the evaluator. Be more or less specific. Also too, by no means, ever use rhythmic redundancies. Contractions aren't essential and shouldn't be there used. Comparisons are as terrible as clichés. Give up ampersands and abbreviations, and so on. Remove commas, that are, not necessary. Parenthetical words however should be together with this in commas. Understatement is all the time the complete best way to put onward earth-shaking thoughts. Give a detailed literary review.

33. Report concluded results: Use concluded results. From raw data, filter the results and then conclude your studies based on measurements and observations taken. Significant figures and appropriate number of decimal places should be used. Parenthetical remarks are prohibitive. Proofread carefully at final stage. In the end give outline to your arguments. Spot out perspectives of further study of this subject. Justify your conclusion by at the bottom of them with sufficient justifications and examples.

34. After conclusion: Once you have concluded your research, the next most important step is to present your findings. Presentation is extremely important as it is the definite medium though which your research is going to be in print to the rest of the crowd. Care should be taken to categorize your thoughts well and present them in a logical and neat manner. A good quality research paper format is essential because it serves to highlight your research paper and bring to light all necessary aspects in your research.

Informal Guidelines of Research Paper Writing

Key points to remember:

- Submit all work in its final form.
- Write your paper in the form, which is presented in the guidelines using the template.
- Please note the criterion for grading the final paper by peer-reviewers.

Final Points:

A purpose of organizing a research paper is to let people to interpret your effort selectively. The journal requires the following sections, submitted in the order listed, each section to start on a new page.

The introduction will be compiled from reference matter and will reflect the design processes or outline of basis that direct you to make study. As you will carry out the process of study, the method and process section will be constructed as like that. The result segment will show related statistics in nearly sequential order and will direct the reviewers next to the similar intellectual paths throughout the data that you took to carry out your study. The discussion section will provide understanding of the data and projections as to the implication of the results. The use of good quality references all through the paper will give the effort trustworthiness by representing an alertness of prior workings.

Writing a research paper is not an easy job no matter how trouble-free the actual research or concept. Practice, excellent preparation, and controlled record keeping are the only means to make straightforward the progression.

General style:

Specific editorial column necessities for compliance of a manuscript will always take over from directions in these general guidelines.

To make a paper clear

· Adhere to recommended page limits

Mistakes to evade

- Insertion a title at the foot of a page with the subsequent text on the next page
- Separating a table/chart or figure - impound each figure/table to a single page
- Submitting a manuscript with pages out of sequence

In every sections of your document

· Use standard writing style including articles ("a", "the," etc.)

· Keep on paying attention on the research topic of the paper

· Use paragraphs to split each significant point (excluding for the abstract)

· Align the primary line of each section

· Present your points in sound order

· Use present tense to report well accepted

· Use past tense to describe specific results

· Shun familiar wording, don't address the reviewer directly, and don't use slang, slang language, or superlatives

· Shun use of extra pictures - include only those figures essential to presenting results

Title Page:

Choose a revealing title. It should be short. It should not have non-standard acronyms or abbreviations. It should not exceed two printed lines. It should include the name(s) and address (es) of all authors.

Abstract:

The summary should be two hundred words or less. It should briefly and clearly explain the key findings reported in the manuscript--must have precise statistics. It should not have abnormal acronyms or abbreviations. It should be logical in itself. Shun citing references at this point.

An abstract is a brief distinct paragraph summary of finished work or work in development. In a minute or less a reviewer can be taught the foundation behind the study, common approach to the problem, relevant results, and significant conclusions or new questions.

Write your summary when your paper is completed because how can you write the summary of anything which is not yet written? Wealth of terminology is very essential in abstract. Yet, use comprehensive sentences and do not let go readability for briefness. You can maintain it succinct by phrasing sentences so that they provide more than lone rationale. The author can at this moment go straight to shortening the outcome. Sum up the study, with the subsequent elements in any summary. Try to maintain the initial two items to no more than one ruling each.

- Reason of the study - theory, overall issue, purpose
- Fundamental goal
- To the point depiction of the research
- Consequences, including definite statistics - if the consequences are quantitative in nature, account quantitative data; results of any numerical analysis should be reported
- Significant conclusions or questions that track from the research(es)

Approach:

- Single section, and succinct
- As a outline of job done, it is always written in past tense
- A conceptual should situate on its own, and not submit to any other part of the paper such as a form or table
- Center on shortening results - bound background information to a verdict or two, if completely necessary
- What you account in an conceptual must be regular with what you reported in the manuscript
- Exact spelling, clearness of sentences and phrases, and appropriate reporting of quantities (proper units, important statistics) are just as significant in an abstract as they are anywhere else

Introduction:

The **Introduction** should "introduce" the manuscript. The reviewer should be presented with sufficient background information to be capable to comprehend and calculate the purpose of your study without having to submit to other works. The basis for the study should be offered. Give most important references but shun difficult to make a comprehensive appraisal of the topic. In the introduction, describe the problem visibly. If the problem is not acknowledged in a logical, reasonable way, the reviewer will have no attention in your result. Speak in common terms about techniques used to explain the problem, if needed, but do not present any particulars about the protocols here. Following approach can create a valuable beginning:

- Explain the value (significance) of the study
- Shield the model - why did you employ this particular system or method? What is its compensation? You strength remark on its appropriateness from a abstract point of vision as well as point out sensible reasons for using it.
- Present a justification. Status your particular theory (es) or aim(s), and describe the logic that led you to choose them.
- Very for a short time explain the tentative propose and how it skilled the declared objectives.

Approach:

- Use past tense except for when referring to recognized facts. After all, the manuscript will be submitted after the entire job is done.
- Sort out your thoughts; manufacture one key point with every section. If you make the four points listed above, you will need a least of four paragraphs.

- Present surroundings information only as desirable in order hold up a situation. The reviewer does not desire to read the whole thing you know about a topic.
- Shape the theory/purpose specifically - do not take a broad view.
- As always, give awareness to spelling, simplicity and correctness of sentences and phrases.

Procedures (Methods and Materials):

This part is supposed to be the easiest to carve if you have good skills. A sound written Procedures segment allows a capable scientist to replacement your results. Present precise information about your supplies. The suppliers and clarity of reagents can be helpful bits of information. Present methods in sequential order but linked methodologies can be grouped as a segment. Be concise when relating the protocols. Attempt for the least amount of information that would permit another capable scientist to spare your outcome but be cautious that vital information is integrated. The use of subheadings is suggested and ought to be synchronized with the results section. When a technique is used that has been well described in another object, mention the specific item describing a way but draw the basic principle while stating the situation. The purpose is to text all particular resources and broad procedures, so that another person may use some or all of the methods in one more study or referee the scientific value of your work. It is not to be a step by step report of the whole thing you did, nor is a methods section a set of orders.

Materials:

- Explain materials individually only if the study is so complex that it saves liberty this way.
- Embrace particular materials, and any tools or provisions that are not frequently found in laboratories.
- Do not take in frequently found.
- If use of a definite type of tools.
- Materials may be reported in a part section or else they may be recognized along with your measures.

Methods:

- Report the method (not particulars of each process that engaged the same methodology)
- Describe the method entirely
- To be succinct, present methods under headings dedicated to specific dealings or groups of measures
- Simplify - details how procedures were completed not how they were exclusively performed on a particular day.
- If well known procedures were used, account the procedure by name, possibly with reference, and that's all.

Approach:

- It is embarrassed or not possible to use vigorous voice when documenting methods with no using first person, which would focus the reviewer's interest on the researcher rather than the job. As a result when script up the methods most authors use third person passive voice.
- Use standard style in this and in every other part of the paper - avoid familiar lists, and use full sentences.

What to keep away from

- Resources and methods are not a set of information.
- Skip all descriptive information and surroundings - save it for the argument.
- Leave out information that is immaterial to a third party.

Results:

The principle of a results segment is to present and demonstrate your conclusion. Create this part a entirely objective details of the outcome, and save all understanding for the discussion.

The page length of this segment is set by the sum and types of data to be reported. Carry on to be to the point, by means of statistics and tables, if suitable, to present consequences most efficiently.You must obviously differentiate material that would usually be incorporated in a study editorial from any unprocessed data or additional appendix matter that would not be available. In fact, such matter should not be submitted at all except requested by the instructor.

Content

- Sum up your conclusion in text and demonstrate them, if suitable, with figures and tables.
- In manuscript, explain each of your consequences, point the reader to remarks that are most appropriate.
- Present a background, such as by describing the question that was addressed by creation an exacting study.
- Explain results of control experiments and comprise remarks that are not accessible in a prescribed figure or table, if appropriate.
- Examine your data, then prepare the analyzed (transformed) data in the form of a figure (graph), table, or in manuscript form.

What to stay away from

- Do not discuss or infer your outcome, report surroundings information, or try to explain anything.
- Not at all, take in raw data or intermediate calculations in a research manuscript.
- Do not present the similar data more than once.
- Manuscript should complement any figures or tables, not duplicate the identical information.
- Never confuse figures with tables - there is a difference.

Approach

- As forever, use past tense when you submit to your results, and put the whole thing in a reasonable order.
- Put figures and tables, appropriately numbered, in order at the end of the report
- If you desire, you may place your figures and tables properly within the text of your results part.

Figures and tables

- If you put figures and tables at the end of the details, make certain that they are visibly distinguished from any attach appendix materials, such as raw facts
- Despite of position, each figure must be numbered one after the other and complete with subtitle
- In spite of position, each table must be titled, numbered one after the other and complete with heading
- All figure and table must be adequately complete that it could situate on its own, divide from text

Discussion:

The Discussion is expected the trickiest segment to write and describe. A lot of papers submitted for journal are discarded based on problems with the Discussion. There is no head of state for how long a argument should be. Position your understanding of the outcome visibly to lead the reviewer through your conclusions, and then finish the paper with a summing up of the implication of the study. The purpose here is to offer an understanding of your results and hold up for all of your conclusions, using facts from your research and generally accepted information, if suitable. The implication of result should be visibly described. Infer your data in the conversation in suitable depth. This means that when you clarify an observable fact you must explain mechanisms that may account for the observation. If your results vary from your prospect, make clear why that may have happened. If your results agree, then explain the theory that the proof supported. It is never suitable to just state that the data approved with prospect, and let it drop at that.

- Make a decision if each premise is supported, discarded, or if you cannot make a conclusion with assurance. Do not just dismiss a study or part of a study as "uncertain."
- Research papers are not acknowledged if the work is imperfect. Draw what conclusions you can based upon the results that you have, and take care of the study as a finished work
- You may propose future guidelines, such as how the experiment might be personalized to accomplish a new idea.
- Give details all of your remarks as much as possible, focus on mechanisms.
- Make a decision if the tentative design sufficiently addressed the theory, and whether or not it was correctly restricted.
- Try to present substitute explanations if sensible alternatives be present.
- One research will not counter an overall question, so maintain the large picture in mind, where do you go next? The best studies unlock new avenues of study. What questions remain?
- Recommendations for detailed papers will offer supplementary suggestions.

Approach:

- When you refer to information, differentiate data generated by your own studies from available information
- Submit to work done by specific persons (including you) in past tense.
- Submit to generally acknowledged facts and main beliefs in present tense.

Administration Rules Listed Before Submitting Your Research Paper to Global Journals Inc. (US)

Please carefully note down following rules and regulation before submitting your Research Paper to Global Journals Inc. (US):

Segment Draft and Final Research Paper: You have to strictly follow the template of research paper. If it is not done your paper may get rejected.

- The **major constraint** is that you must independently make all content, tables, graphs, and facts that are offered in the paper. You must write each part of the paper wholly on your own. The Peer-reviewers need to identify your own perceptive of the concepts in your own terms. NEVER extract straight from any foundation, and never rephrase someone else's analysis.

- Do not give permission to anyone else to "PROOFREAD" your manuscript.

- Methods to avoid Plagiarism is applied by us on every paper, if found guilty, you will be blacklisted by all of our collaborated research groups, your institution will be informed for this and strict legal actions will be taken immediately.)
- To guard yourself and others from possible illegal use please do not permit anyone right to use to your paper and files.

Criterion for Grading a Research Paper (Compilation) by Global Journals Inc. (US)

Please note that following table is only a Grading of "Paper Compilation" and not on "Performed/Stated Research" whose grading solely depends on Individual Assigned Peer Reviewer and Editorial Board Member. These can be available only on request and after decision of Paper. This report will be the property of Global Journals Inc. (US).

Topics	Grades		
	A-B	**C-D**	**E-F**
Abstract	Clear and concise with appropriate content, Correct format. 200 words or below	Unclear summary and no specific data, Incorrect form Above 200 words	No specific data with ambiguous information Above 250 words
Introduction	Containing all background details with clear goal and appropriate details, flow specification, no grammar and spelling mistake, well organized sentence and paragraph, reference cited	Unclear and confusing data, appropriate format, grammar and spelling errors with unorganized matter	Out of place depth and content, hazy format
Methods and Procedures	Clear and to the point with well arranged paragraph, precision and accuracy of facts and figures, well organized subheads	Difficult to comprehend with embarrassed text, too much explanation but completed	Incorrect and unorganized structure with hazy meaning
Result	Well organized, Clear and specific, Correct units with precision, correct data, well structuring of paragraph, no grammar and spelling mistake	Complete and embarrassed text, difficult to comprehend	Irregular format with wrong facts and figures
Discussion	Well organized, meaningful specification, sound conclusion, logical and concise explanation, highly structured paragraph reference cited	Wordy, unclear conclusion, spurious	Conclusion is not cited, unorganized, difficult to comprehend
References	Complete and correct format, well organized	Beside the point, Incomplete	Wrong format and structuring

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ISSN 9755896