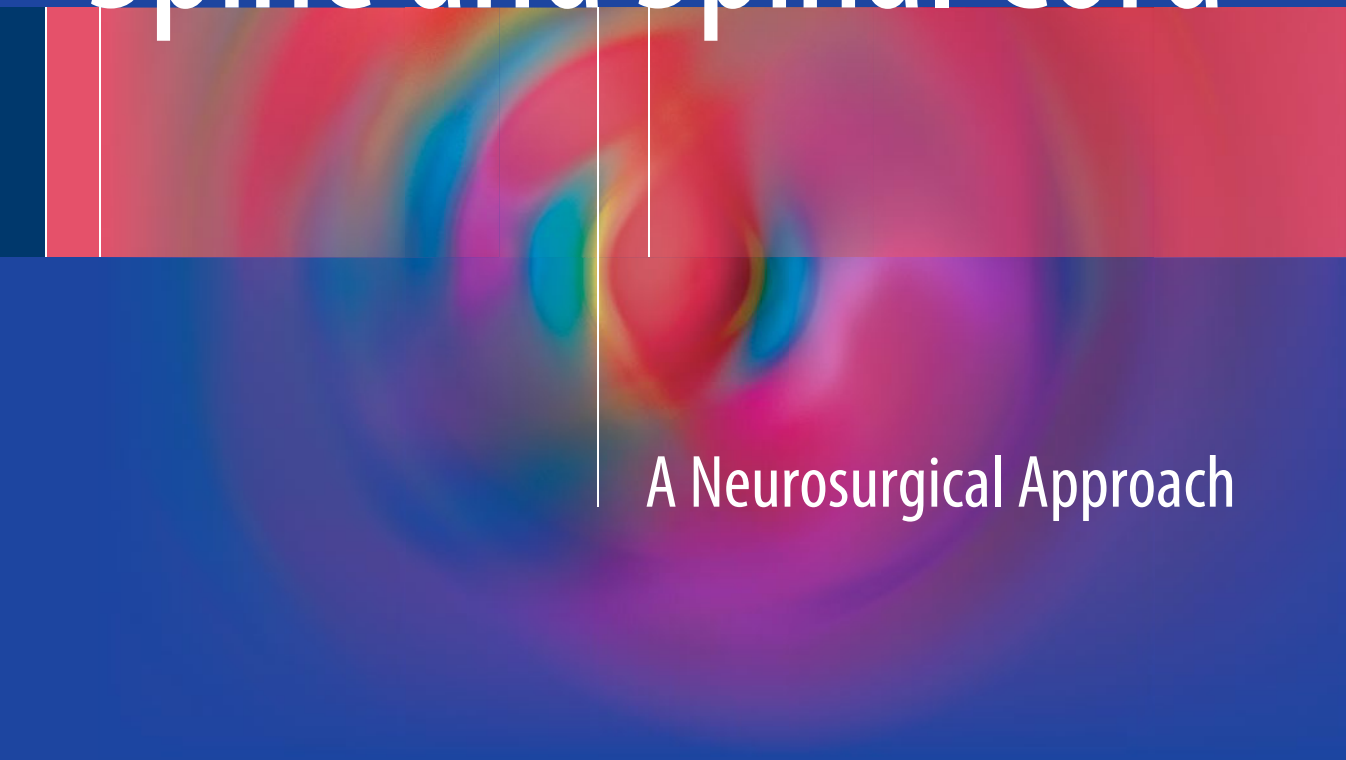
Erik Van de Kelft
Editor

Surgery of the Spine and Spinal Cord



A Neurosurgical Approach

EXTRAS ONLINE

Springer

Surgery of the Spine and Spinal Cord

Erik Van de Kelft
Editor

Surgery of the Spine and Spinal Cord

A Neurosurgical Approach

Springer

Editor
Erik Van de Kelft
Sint-Niklaas
Belgium

ISBN 978-3-319-27611-3 ISBN 978-3-319-27613-7 (eBook)
DOI 10.1007/978-3-319-27613-7

Library of Congress Control Number: 2016934596

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer International Publishing AG Switzerland

Contents

Contributors

Franck Accadbled, PhD Department of Neurosurgery,
Hôpital des Enfants, Toulouse, France

Xavier Armoiry, MD Department of PHRC Steering committee,
Hospices Civils de Lyon, Lyon, France

Richard Assaker, MD, PhD Department of Neurosurgery, CHRU de Lille,
Lille, France

Lukasz Augsburg, MD Department of Radiology,
Antwerp University Hospital, University of Antwerp,
Antwerp, Belgium

Céderic Barrey, MD, PhD Department of Neurosurgery
and Spine surgery, P. Wertheimer Hospital, Lyon, France

Uli H. Beese, MD, PhD Department of Anesthesiology,
University Medical Centre Groningen, University of Groningen,
Groningen, The Netherlands

Edward C. Benzel, MD Center for Spine Health, Neurological Institute,
Cleveland Clinic, Cleveland, OH, USA

Julien Berthiller, MD Department of PHRC Steering Committee,
Hospices Civils de Lyon, Lyon, France

Christopher Brenke, MD Department of Neurosurgery,
Knappschaftskrankenhaus Bochum, Ruhr-University of Bochum,
Bochum, Germany

Helena Brisby, MD, PhD Department of Orthopaedic Surgery,
Institute of Clinical Sciences, Sahlgrenska Academy,
University of Gothenburg, Gothenburg, Sweden

Department of Orthopaedics, Sahlgrenska University Hospital,
Gothenburg, Sweden

Jacques Brotchi, MD, PhD Department of Neurosurgery,
Erasme Hospital, Brussels, Belgium

Michaël Bruneau, MD, PhD Department of Neurosurgery,
Erasme Hospital, Brussels, Belgium

Mohamad Bydon, MD Department of Neurosurgery,
John Hopkins Hospital, Baltimore, MA, USA

Jean-Claude Cajot, MD Department of Neurosurgery, Erasme Hospital,
Brussels, Belgium

Ken Carpentier, MD Department of Radiology,
Antwerp University Hospital, University of Antwerp,
Antwerp, Belgium

Paulo Tadeu Maia Cavali, MD Department of Scoliosisi, associaçao de
Assisntência à Criança Deficiente Unversidade Estadual de Caminas
(Unicampt Campinas), Hospital Alemao Oswalda Cruz (HAOC),
Sao Paulo, Brazil

Erwin M.J. Cornips, MD Department of Neurosurgery,
Maastricht UMC+, Maastricht, The Netherlands

Kristiaan D'Août, PhD Department of Musculoskeletal Biology,
Institue of Ageing and Chronic Disease, University of Liverpool,
Liverpool, UK

Agnes d'Entremont, BEng, MASc, PhD Department of Orthopaedics,
Faculty of Medicine, University of British Columbia, Vancouver, Canada

Frank De Belder, MD Department of Radiology, Antwerp University
Hospital and University of Antwerp, Antwerp, Belgium

Bruno De Potter, MD Department of Radiology,
Antwerp University Hospital, University of Antwerp,
Antwerp, Belgium

Daniela Diesing, MD Department of Neurosurgery, Regional Spine Center,
Moers/Kempen, Germany

Peter Dubruel, PhD Department of Polymer Chemistry and Biomaterials
Research Group (PBM-Ugent), University of Ghent, Ghent, Belgium

Antonio A. Faundez, MD Department of Neurosurgery, Hôpital La Tour en
Hôpitaux Universitaires de Genève, Genève, Switzerland

Marguerite Faure, MD Department of Radiology, Antwerp University
Hospital and University of Antwerp, Antwerp, Belgium

Roque Fernandez, MD Department of Spine Surgery, Hochtaunuskliniken
and Neurosurgical Associates, Bad Homburg, Germany

Richard G. Fessler, MD, PhD Department of Neurosurgery,
Rush University Medical Center, Chicago, IL, USA

Vincent Fiere, MD Department of PHRC Steering Committee,
Hospices Civils de Lyon, Lyon, France

Charles G. Fisher, MD Department of The Combined Neurosurgical
and Orthopedic Spine Program, Vancouver Coastal Health and the University
of British Columbia, Vancouver, BC, Canada

Patrick Fransen, MD Department of Neurosurgery, Clinique du Parc Léopold – Chirec, Brussels, Belgium

Bernard George, MD Department of Neurosurgery, Lariboisière Hospital, Paris, France

Carter S. Gerard, MD Department of Neurosurgery, Rush University Medical Center, Chicago, IL, USA

Ziya L. Gokaslan, MD Department of Neurosurgery, The Warren Alpert Medical School of Brown University, Providence, RI, USA

Gerbrand J. Groen, MD, PhD Department of Anesthesiology, University Medical Centre Groningen, University of Groningen, Groningen, The Netherlands

Rob J.M. Groen, MD, PhD Department of Neurosurgery, University Medical Centre Groningen, University of Groningen, Groningen, The Netherlands

Jef Huyskens, MD Department of Radiology, Antwerp University Hospital and University of Antwerp, Antwerp, Belgium

Ricky Kalra, MD Department of Neurosurgery Clinical Neurosciences Center, University of Utah, Salt Lake City, UT, USA

Manish K. Kasliwal, MD, PCh Department of Neurosurgery, Rush University Medical Center, Chicago, IL, USA

Thomas Kosztowski, MD Department of Neurosurgery, John Hopkins Hospital, Baltimore, MA, USA

Virginie Lafage, MD Department of PHRC Steering Committee, Hospices Civils de Lyon, Lyon, France

New York Hospital for Joint Disease, New York, NY, USA

Patricia Larouche, MD, FRCSC, MHSc Department of Orthopaedic Surgery, University of British Columbia, Vancouver, BC, Canada

Department of Orthopaedics, Faculty of Medicine, British Columbia Children's Hospital, Vancouver, BC, Canada

Jean-Charles Le Huec, MD Department of Neurosurgery, Hôpital Pellegrin, Bordeaux, France

Richard J. Mannion, FRCS (Surgical Neurology), PhD Department of Neurosurgery, Cambridge University Hospitals, Cambridge, UK

Frederic Martens, MD Department of Neurosurgery, OLV Hospital, Aalst, Belgium

Tobias A. Mattei, MD Department of Neurosurgery, Brain Spine Center, InvisionHealth, Buffalo, NY, USA

Koen Melis, MD Department of Medical and Molecular Imaging, AZ Nikolaas, Sint Niklaas, Belgium

Ehud Mendel, MD Department of Neurosurgery, Ohio State University Medical Center – James Cancer Center, Columbus, OH, USA

Jeffrey P. Mullin, MD Department of Neurological Institute, Cleveland Clinic, Cleveland, OH, USA

Kristoff Muylle, MD Department of Medical and Molecular Imaging, AZ Nikolaas, Sint Niklaas, Belgium

Kishore Mulpuri, MBBS, MS(Ortho), MHSc(Epi) Department of Orthopaedic, Faculty of Medicine, British Columbia Children's Hospital, University of British Columbia, Vancouver, Canada

Paul M. Parizel, MD, PhD Department of Radiology, Antwerp University Hospital, University of Antwerp, Antwerp, Belgium

Gilles Perrin, MD Department of Neurosurgery and Spine Surgery, P. Wertheimer Hospital, Lyon, France

Nicolas Plais, MD Department of Neurosurgery, Hôpital Pellegrin, Bordeaux, France

Ingrid Preissl, MD Department of Spine Surgery, Hochtaunuskliniken and Neurosurgical Associates, Bad Homburg, Germany

Adam Prince, BS Department of Neurosurgery, Drexel University College of Medicine, Philadelphia, PA, USA

Amir Qaseem, MD, PhD, MHA, FACP Department of Clinical Policy, American College of Physicians, Philadelphia, PA, USA

Frank Ramon, MD Department of Medical and Molecular Imaging, AZ Nikolaas, Sint Niklaas, Belgium

Julien Rigal, MD Department of Neurosurgery, Hôpital Pellegrin, Bordeaux, France

Mattéo Riva, MD Department of Neurosurgery, Erasme Hospital, Brussels, Belgium

Daniel Rosenthal, MD Department of Spine Surgery, Hochtaunuskliniken and Neurosurgical Associates, Bad Homburg, Germany

Pierre Roussouly, MD Department of Orthopaedic and Spine Surgery, Clinique des Massues, Lyon, France

Khalid M.I. Salem, MD Department of The Combined Neurosurgical and Orthopedic Spine Program, Vancouver Coastal Health and the University of British Columbia, Vancouver, BC, Canada

Jérôme Sales de Gauzy, MD Department of Neurosurgery, Hôpital des Enfants, Toulouse, France

Judith Scheman, PhD Center for Neurological Restoration, Neurological Institute, Cleveland Clinic, Cleveland, OH, USA

Kai-Michael Scheufler, MD Department of Neurosurgery, Regional Spine Center, Moers/Kempen, Germany

Fréderic Schils, MD Department of Neurosurgery, Cinique Générale Beaulieu – Clinique La Colline, Geneva, Switzerland

Meic H. Schmidt, MD, MBA. Department of Neurosurgery, Clinical Neurosciences Center, University of Utah, Salt Lake City, UT, USA

Kristen Schmieder, MD Department of Neurosurgery, Knappschaftskrankenhaus Bochum, Ruhr-University of Bochum, Bochum, Germany

Laura A. Snyder, MD Department of Neurosurgery, Rush University Medical Center, Chicago, IL, USA

Lee A. Tan, MD Department of Neurosurgery, Rush University Medical Center, Chicago, IL, USA

Alisson R. Teles, MD Department of Neurosurgery, Hospital Sao José, Santa Case de Porto Alegre, Porto Alegre, Brazil

Hugo Thienpont, Ir, PhD Department of Brussels-Photonics Research Group (B-PHOT), University of Brussels, Brussels, Belgium

George Thompson, MD Department of Pediatric Orthopaedics, Rainbow Babies and Children's Hospitals, University Hospitals Case Medical Center, Case Western Reserve University, Cleveland, OH, USA

Vincent C. Traynelis, MD Department of Neurosurgery, Rush University Medical Center, Chicago, IL, USA

Tsung-Hsi Tu, MD Department of Neurosurgery, Taipei Veterans General Hospital, Faculty of Medicine, National Yang-Ming University, Taipei, Taiwan

Wim Van Biesen, MD, PhD Department of Renal Division, Ghent University Hospital, Ghent, Belgium

Jean Pierre Van Buyten, MD Multidisciplinary Pain Center AZ Nikolaas, Sint Niklaas, Belgium

Erik Van de Kelft, MD, PhD Department of Neurosurgery, AZ Nikolaas, Sint Niklaas, Belgium

Luc Van Den Hauwe, MD Department of Radiology, Antwerp University Hospital & University of Antwerp, Antwerp, Belgium

Johan W.M. Van Goethem, MD, PhD Department of Radiology, Antwerp University Hospital and University of Antwerp, Antwerp, Belgium

Department of Medical and Molecular Imaging, AZ Nikolaas, Sint Niklaas, Belgium

Jasper Van Hoorick, MSc Department of Polymer Chemistry and Biomaterials Research Group (PBM-Ugent), University of Ghent, Ghent, Belgium

Department of Brussels-Photonics Research Group (B-PHOT), University of Brussels, Brussels, Belgium

Sandra Van Vlierberghe, PhD Department of Polymer Chemistry and Biomaterials Research Group (PBM-Ugent), University of Ghent, Ghent, Belgium

Department of Brussels-Photonics Research Group (B-PHOT), University of Brussels, Brussels, Belgium

Caroline Venstermans, MD Department of Radiology, Antwerp University Hospital and University of Antwerp, Antwerp, Belgium

Jean Marc Vital, MD Department of PHRC Steering Committee, Hospices Civils de Lyon, Lyon, France

Department of Neurosurgery, CHU Pellegrin, Bordeaux, France

Michael Winking, MD, PhD Department of Neurosurgery, ZWO Spine Center Osnabrueck, Osnabrueck, Germany

Jean-Paul Wolinsky, MD Department of Neurosurgery, Oncology and Orthopaedic Surgery, Johns Hopkins University, Baltimore, MA, USA

Jau-Ching Wu, MD, PhD Department of Neurosurgery, Taipei Veterans General Hospital, Taipei, Taiwan

Introduction to Surgery of the Spine and Spinal Cord. A Neurosurgical Approach

When Dr. Erik Van de Kelft asked me to write an introduction to his book *Surgery of the Spine and Spinal Cord. A Neurosurgical Approach* I immediately accepted because the spine represents a very large part of our activities besides brain surgery. I like the concept of spine surgery and the idea to invite orthopedic surgeons and neurosurgeons to contribute to this book and to share their opinions. In several pathologies, the expertise of both neurosurgeons and orthopedic surgeons brings benefit to patients and health care. Spine spectrum is growing year after year. Low back pain represents the first cause of work disabilities in patients less than 40 years old in western countries.

When I look back to the past, I may say that imaging has revolutionized diagnosis and quality of life after surgery in most pathologies from spondylotic myelopathy to intramedullary tumors. New surgical approaches and technologies have also tremendously improved our results.

The future is promising with disc repair, but we should invest more in the prevention of low back pain. On the other hand, stem cells therapy could drastically change our possibilities to approach many spinal cord diseases.

Coming back to the book, I like to congratulate Dr. Erik Van de Kelft for succeeding to get contributions from most well-known neuroradiologists, neurosurgeons, and orthopedic surgeons. This book should be consulted/read by every spine surgeon in the world. It offers the most important insights, detailed descriptions of surgical techniques and accurate recommendations for good clinical practice today and in the near future. Therefore, this book will soon become a classic on this topic and the reference for spine surgeons.

Jacques Brotchi, MD, PhD
Emeritus Professor of Neurosurgery
Erasme Hospital, Brussels, Belgium
Co-founder of World Neurosurgery
Honorary President of the World Federation
of Neurosurgical Societies

Part I

General Considerations

Why Another Book on Spine Surgery?

1

Erik Van de Kelft

In this era of abundant digital information, where most of us have the opportunity to travel around the world and see colleagues at work, while spine courses and congresses are organized in all parts of our globe and in times where most of us read regularly specialized journals, books seem to become an anachronism. It is, however, my opinion that they are not. Scientific books can bundle reflections on one specific theme, in this case, spine surgery. Although many books have already been published in this field, it is my belief that much more will come in the future. The information we gather during our daily work is so overwhelming that, at times, we seek a relaxing moment for reflection and synthesis. This book has been edited with this focus in mind.

I am convinced that we will live thrilling times, when considering spine disorders and their surgical treatment. In the past, we all were able to acquire surgical skills and knowledge regarding techniques. This evolution of surgical skills and techniques, however, is not always welcomed, particularly by those who have to pay for it. They, but we also, are looking for more value in what we do. Health-care authorities, insurers and taxpayers are forcing us to change from a volume to a value-based decision-making process. Today, we reach the point that if no evidence exists about a surgical treatment for a given spinal disorder, the reimbursement might become troublesome. While training our surgical skills, we (most of us) forgot to measure the outcomes of our work. While focusing on the surgical work, there was not sufficient interest in refining the diagnostic procedures for chronic (low) back pain. To improve the benefits patients experience from our work, we will have to invest in other things than just surgical skills; innovation, research, evidence and education will all be key factors for a healthy future.

This book starts with innovation. I was very excited when reading the chapter on tissue engineering. It is amazing what this technology might offer in the near future! We as spine surgeons know about spinal disorders and know our patients. Therefore, we should get involved in this emerging technology. During the next few years, innovation may rather focus on the prevention of degeneration of the spine, rather than its restoration. The innovation should be directed towards the patient's individual needs. At present, the ability to make patient-specific tissue engineered scaffolds to replace the nucleus pulposus, the annulus fibrosus or even the whole intervertebral disk does exist. Further in this book, there is a chapter dedicated to the innovative technique of manufacturing individualized patient-specific rods to restore the sagittal balance of the spine.

E. Van de Kelft, MD, PhD
Department of Neurosurgery, AZ Nikolaas,
Sint Niklaas, Belgium
e-mail: erik.vandekelft@aznikolaas.be;
Erik.vandekelft@telenet.be

E. Van de Kelft (ed.), *Surgery of the Spine and Spinal Cord. A Neurosurgical Approach*.
DOI 10.1007/978-3-319-27613-7_1

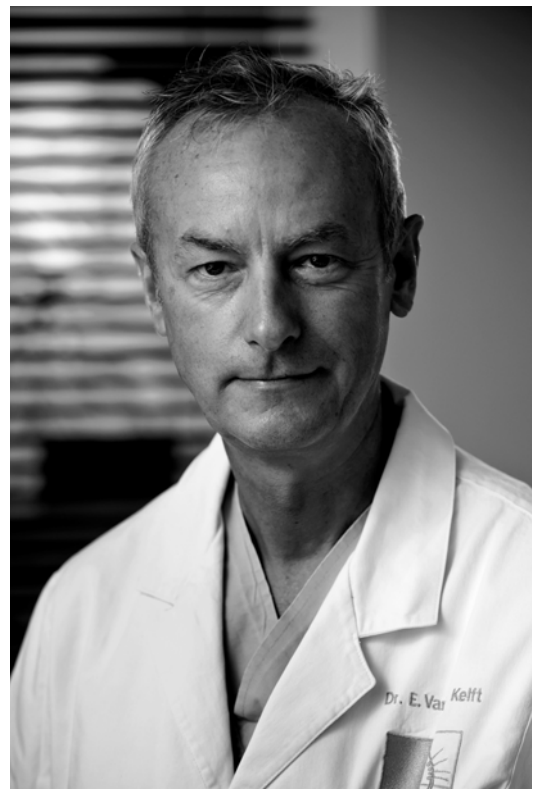
In the chapter on chronic low back pain, we learn that after all these years of research, we still have a knowledge gap of over 80 % concerning the correct diagnosis. More research in the different pain mechanisms and the diagnostic procedures is mandatory to understand the different pathophysiological processes. If we do not understand the pain mechanism and cannot identify the pain generator, surgical treatment should not be an option. Different pain mechanisms and the appropriate use of advanced imaging techniques are well described in these chapters. These will be important tools to help us as surgeons better diagnose our patients.

In this book, the authors and myself made a great deal of efforts to summarize the amount of evidence for some surgical treatments. It is hard to admit, but, for most indications, evidence does not exist (sometimes it has never been measured) or is rather weak. Since evidence will be one of the key points when evaluating the effectiveness of our surgery, I added two splendid chapters on this theme. We, spine surgeons, should be armed with the knowledge of what evidence-based medicine means, why it sometimes is not evident to demonstrate evidence and why, without evidence, some treatments might be valuable. In the 'blue boxes', at the end of some chapters, I tried to summarize the evidence, if it exists.

Education does not mean that we are able to absorb all new data the 'spine treatment community' worldwide continues to develop and publish every day. Education means the continued self-development of ourselves as surgeons, and we need to be able to easily access the information that brings valuable knowledge and skill sets. This book, therefore, can be considered as another educational brick to build further on the temple of science, in which the spine pathology and its treatment should reside.

To end with, why a 'neurosurgical approach'? Because the publisher, Springer, asked me to edit a book on spine surgery with a neurosurgical scope. As you will notice when looking at the list of the many contributors working in four different continents, besides neurosurgeons, there are also many orthopaedic surgeons. While editing this book, I was amazed how spine surgery is so multifaceted. And this book is only a selection of pathologies; we excluded trauma, infection and paediatric spine problems. The knowledge of spine disorders, the surgical skills and the challenges I mentioned earlier are so demanding for one person that the evolution will probably make us work more in teams, where orthopaedic and neurosurgeons work together. It furthermore becomes hard to accept that one is excellent in spine surgery, besides other skills. For all these reasons, I used the word 'spine surgeon' throughout this book.

This book has been edited for the spine surgeon who wants to accept the challenges of today and those of the future!



Evolution of the Vertebral Column

2

Kristiaan D'Août

Contents

2.1 Introduction

The human vertebral column (or the spine) serves two main functions: a biomechanical one and a protective one. The spine gives the body longitudinal support (while retaining a degree of mobility), connects the head and limbs, offers muscle attachment sites and protects the spinal cord. In this chapter, we will explore how these functions have developed during evolution and have led to the very specific structure that is unique to the only habitual striding biped among mammals: man.

2.2 The Origin of the Basic Mammalian Vertebral Structure

Many aquatic animals do not need a structural support of the body, e.g. jellyfish, which are neutrally buoyant and move by jet propulsion. Other animals, e.g. many molluscs and insects, use some type of exoskeleton. Vertebrates, however, are named after their endoskeleton with a segmented vertebral column. If we want to understand its origins, we have to go back to the parental group of the vertebrates: the chordates. In the most primitive members of this group, longitudinal body support is provided by the notochord, an unsegmented structure consisting of fibrous connective tissue around a core of fluid.

K. D'Août, PhD
Department of Musculoskeletal Biology, Institute of Ageing and Chronic Disease, University of Liverpool, Liverpool, UK
e-mail: kristiaan.daout@liverpool.ac.uk

E. Van de Kelft (ed.), *Surgery of the Spine and Spinal Cord. A Neurosurgical Approach*.
DOI 10.1007/978-3-319-27613-7_2

This 'hydrostatic skeleton', which can be seen in extant hagfishes and lancelets, allows for longitudinal stiffness but provides no muscular attachment sites. The notochord can still be seen during embryonic development in all vertebrates and defines the axis of the body, around which the axial skeleton forms. It is also seen in the adult stages of some vertebrates (e.g. lungfish), and it persists as the nucleus pulposus in mammals, including humans.

Segmented vertebrae first showed as ventral (haemal) and dorsal (neural) arches. They served to protect, respectively, blood vessels and the neural tube. The supportive function of the spine only came later.

The next evolutionary stage was the development of two centra (the pleurocentrum and the intercentrum), which supported the ventral arches but did not surround he notochord completely. Such arrangement can be seen in primitive gnathostomes [1], and it fundamentally persists in all of the vertebrae we can see to date – all consisting of arches and centra (Fig. 2.1). Evolution has acted upon these structures; some have enlarged, while others have reduced, explaining for a large part the vertebral diversity we can observe today.

During the course of evolution, the vertebrae became strong units (particularly because of the enlarged centra) replacing the notochord as the fundamental support structure. They also became regionally differentiated. Fish have two regions (trunk and caudal), while amniotes (amphibians, reptiles, birds and mammals) have up to five regions: cervical, thoracic, lumbar, sacral and caudal, with varying vertebral numbers in these regions.

In amniotes, the pleurocentrum dominates and forms the body of each vertebra. The intercentra initially form the cartilaginous intervertebral disks but in mammals, they only remain present as the rib's capitulum. The centra link up into an axial vertebral column assisted by interspinal ligaments. The articular shape defines the intervertebral articular surfaces and thus largely determines in which plane movement is allowed. Articular shapes strongly differ between animal groups and even within a single body, while many show high intervertebral mobility due to their biconcave or concave/convex joint shapes; in mammals, the centra have flat articulations, which have reduced mobility but can withstand high compressive forces.

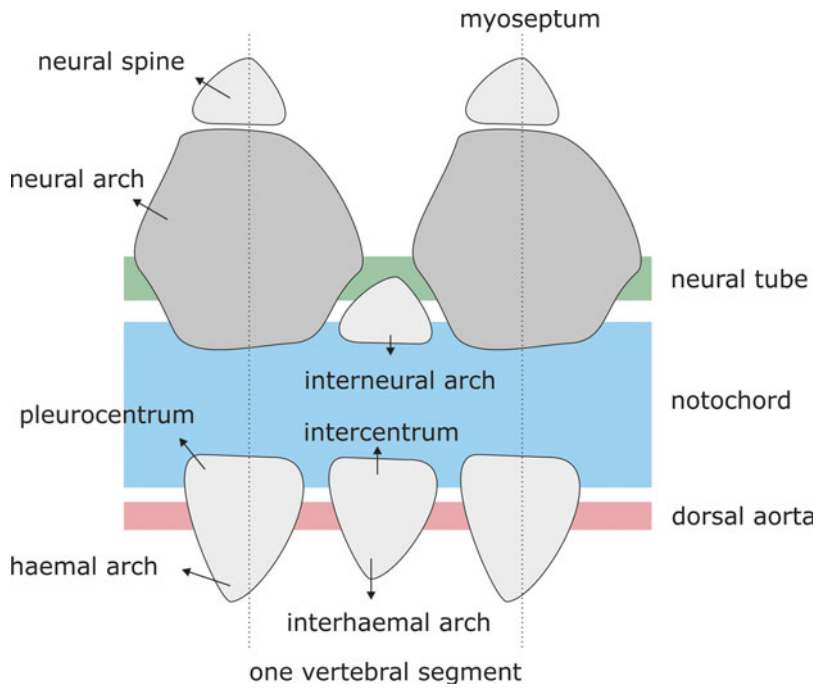


Fig. 2.1 Schematic representation of the primitive vertebral structure, here in a gnathostome [1]

In fish, lizards and snakes, the movement of the spine is characterised by a lateral undulation. In crocodiles, the spine can, in addition, move dorsoventrally as can be seen in mammals. Dolphins, reflecting their mammalian heritage, move in the water with a dorsoventral movement of their spine in contrast to fish.

During evolution, the ventral arch decreases in importance or disappears (e.g. in mammals, it is only occasionally found in the tail), while the dorsal arch dominates. The dorsal arch persists in mammals, including humans, as the vertebral arch. It serves to protect the spinal cord, it provides attachment sites for both hypaxial and epaxial musculature and it provides attachment for numerous processes.

In addition to the centrum and arches, vertebrae can develop a number of processes – apophyses. Some of these (the pre- and postzygapophyses) provide resistance to twisting.

Other apophyses carry ribs, which serve locomotor, respiratory and protective functions. Basapophyses are paired remnants of the haemal arch bases, which may articulate with the ventral ribs of fish (which are probably homologous to the haemal arches). Tetrapods only retain dorsal ribs (termed the trunk ribs), which have a bicapital articulation. The ventral head (capitulum) articulates with the pleurocentrum (in most reptiles and birds) or, in mammals, between the centra. The dorsal head (tuberculum) articulates with the diapophysis, a process on the neural arch.

Processes also change between species and between regions, e.g. in mammals, where processes disappear towards the end of the tail and only centra remain.

In mammals, the vertebral column is highly regionalised, and vertebral numbers are much more conservative than in other groups.

Typically (with very few exceptions), there are seven cervical vertebrae, of which the first two (as in other amniotes), the atlas and the axis, are highly specialised in order to support the head while allowing for great range of motion. There are typically 15–20 thoracic and lumbar vertebrae (combined) and 2–3 sacral vertebrae (5 in humans). The number of caudal vertebrae is highly variable [2]. The basic structure of the human vertebrae is similar to that of other mammals.

At this point, it should be clear that the evolution of the vertebrae is complex, with specific components gaining importance while others are reduced, depending on the phylogenetic history and locomotor demands of the animal. We will therefore outline first some of the most important differences between the human spine and the non-human primate spine and subsequently focus on the evolution of the spine in hominins.

2.3 The Primate Spine

Humans are hominoid primates (apes), and it is instructive to consider the extant primate spine as a model or analogue to understand our ancestral spine structure, which later became adapted to our specific life style and, most importantly, our unique form of locomotion – habitual striding bipedalism (for details on the evolution of primate morphology, we refer to the literature [3]).

The generalised primate vertebra consists of a well-developed body with a neural (also named dorsal or vertebral) arch. The base of this arch is formed by the paired pedicles, joining into the paired laminae onto which the spinal process sits (which is unpaired but might end in double tubercles; [4]). The spinous process can vary in its length, strength and direction.

Laterally, the neural arch possesses transverse processes and articular processes (zygapophyses).

The intervertebral disks are important, and the makeup is approximately one fourth of the presacral spine length in humans, but they vary in thickness and shape.

2.3.1 Vertebral Structure Varies Across the Regions in All Primates

In the cervical (C) region, the vertebral foramen is at its largest, and there is a transverse foramen through the transverse processes. The two first vertebrae, the atlas (C1) and the axis (C2), are atypical: they are much derived, and there is no

intervertebral disk between them. The atlas has no body or spinous process and transmits the weight of the head from the two occipital condyles (allowing movement in the sagittal plane, as in nodding 'yes') onto the axis. The axis has cranially oriented dens, which articulate firmly with what is left of the ventral arch of the atlas. Movement between the atlas and the axis is rotation along the longitudinal axis (as in 'no'). The orientation of the dens differs among primates. It is retroflexed in typical pronograde quadrupeds, which (together with the position of the foramen magnum) positions the head rather in line with the vertebral column. The dens is slightly bent in knuckle walkers (African great apes who have much longer forelimbs than hind limbs) and completely along the longitudinal axis in the orthograde habitual bipeds (humans), helping to balance the head vertically into the vertebral column.

The typical cervical vertebrae (C3–C6) have kidney-shaped bodies in a cross-sectional view and possess uncinate processes, which are facing cranially and articulate with the previous vertebra's body.

C7 is atypical and has a very long spinous process (which is not bifid, unlike in the typical cervical vertebrae). All primates, like all mammals, possess seven cervical vertebrae.

The thoracic (T) vertebrae are typically heart shaped in cross section and bear ribs. In order to do so, they have facets on the body (two demifacets per side, one cranially and one caudally) and on the transverse processes. A rib typically articulates with a demifacet of its vertebra a demifacet of the vertebra above, and its tubercle articulates with the transverse process. However, the ribs of the first thoracic vertebra, in humans, and the last two thoracic vertebrae, in humans as well as apes, articulate only via a single facet, not two demifacets (Fig. 2.2).

Caudally, the thoracic vertebral bodies become bigger (longer and wider), the rate at which varies between species. Neural arch size often (but not always) decreases.

The shape of the superior and inferior articular process is of great interest because of its functional meaning. While oriented almost in the frontal plane cranially, then there is a sudden change to the lumbar arrangement (i.e. angled steeply) at the transitional (or diaphragmatic) vertebra [5, 6], making the subregions very stable. The pre-diaphragmatic region allows for rotational movements, whereas the post-diaphragmatic region does not.

Usually, the functional region of the thoracic region is shorter than the rib-bearing region. The ribs are very interesting from a comparative point of view but fall outside the scope of this chapter. The spinous processes are usually oriented caudally, to varying degrees (e.g. in humans more steeply than in non-human primates).

The lumbar (L) region possesses vertebrae with laterally projecting transverse processes and facet joints which interlock tightly between two vertebrae. This arrangement increases stability and limits rotational motion (but allowing flexion and extension). Some primates have accessory processes on the posterior articular processes, locking with the anterior articular process of the next (more caudal) vertebra. Spinous processes in the lumbar region are usually well developed and oriented cranially (not caudally, as in the thoracic region).

It should be noted that the lumbar vertebral bodies are more robust in primates than in other mammals, which has been related to their more upright postures (if not habitual) [7].

In the sacral (S) region, the vertebral bodies, the articulations between the neural arches and the neural spines (partly or completely) are fused, and there are no intervertebral disks. Therefore, the sacrum is a rigid region.

The caudal region is highly variable in primates. Only the first few caudal vertebrae have a fully developed neural arch, but most also have ventral arches (connected to the body by ligaments) that protect the caudal artery.

While the basic anatomy and function of the regions, outlined here, holds for all primates, substantial variation exists within primate taxa, and we will here outline some of this variation in hominoids (apes, including humans), stating how they differ from other primates.

One main point of variation is in the number of vertebrae per region, which differs inter- (and sometimes intra-) specifically. We will focus on

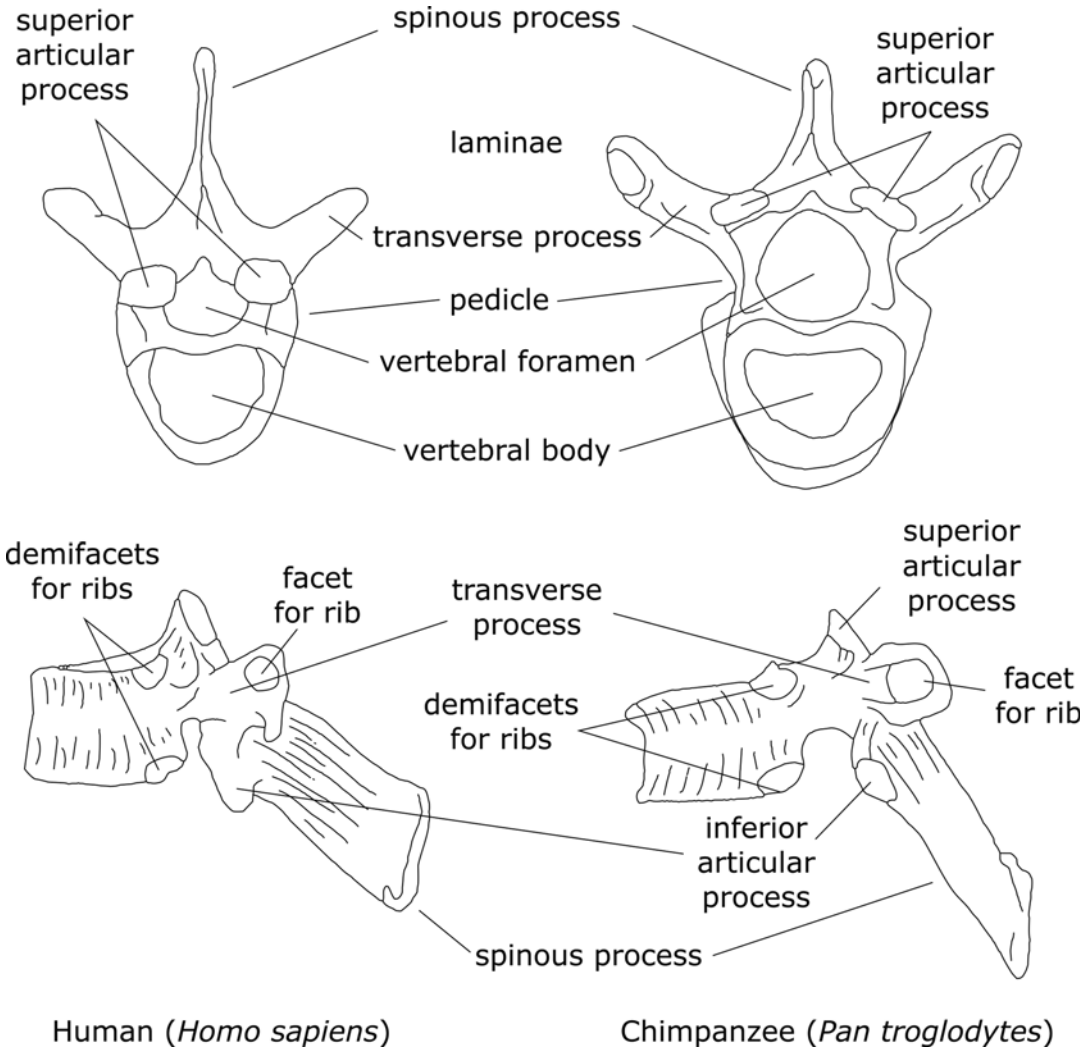


Fig. 2.2 Schematic drawing of the sixth thoracic vertebra (T6) of a chimpanzee and a human. *Top*, axial view; *bottom*, lateral view (After Aiello and Dean [8])

the thoracic, lumbar and sacral regions, since the cervical region is highly conservative, even across mammals, with seven vertebrae, and the caudal region is very variable (e.g. ranging from no caudal vertebrae in some gibbons to more than 30 in the robust prehensile tail of spider monkeys) but less relevant for humans. Interestingly, the total number of thoracic, lumbar and sacral vertebrae is usually 22 across apes and even monkeys [9], and it is the distribution between regions that differs (Table 2.1, adapted from after Schultz [10]).

Apes, as well as other non-human primates, usually have more than 12 thoracic vertebrae (e.g. up to 14 in chimpanzees, *Pan*, and up to 16 in the New World monkeys *Alouatta*). For the lumbar region, it is interesting that the apes, our closest relatives, have less vertebrae than humans (typically three or four), which increased stiffness is associated with the demands of climbing, but primates in general often have more than five lumbar vertebrae (e.g. up to nine in the Old World monkeys *Presbytis*). A long lumbar region may thus be the primitive primate condition, with an independent reduction in vertebral numbers in apes (see [10–12]). It has been stated in the past that early hominins had six lumbar vertebrae but

Table 2.1 Vertebral numbers per region in some primates

	Thoracic	Lumbar	Sacral	Caudal	TL total	TLS total
Human (*Homo*)	12.0	5.0	5.2	4.0	17	22.2
	(11–13)	(4–6)	(4–7)	(2–5)		
Chimpanzee (*Pan*)	13.2	3.6	5.7	3.3	16.8	22.5
	(12–14)	(3–4)	(4–8)	(2–5)		
Gorilla (*Gorilla*)	13.0	3.6	5.7	3	16.6	22.3
	(12–14)	(3–5)	(4–8)	(1–5)		
Orang-utan (*Pongo*)	11.9	4.0	5.4	2.6	15.9	21.3
	(11–13)	(3–5)	(4–7)	(1–5)		
Gibbon (*Hylobates*)	13.1	5.1	4.6	2.7	18.2	22.8
	(12–14)	(4–6)	(3–6)	(0–6)		
Macaque (*Macaca*)	12.1	6.9	3.0	17.0	19	22.0
	(12–13)	(6–8)	(2–4)	(5–28)		
Spider monkey (*Ateles*)	13.8	4.2	3.0	31.1	18	21.0
	(13–15)	(4–5)	(2–4)	(28–35)		

After Schultz [10]

[6] have shown that they had five, still one more than typical for great apes.

The number of sacral vertebrae within apes is somewhat variable but usually 5–6. Thus, compared to the other apes, humans typically have an extended lumbar region (+1 or 2 vertebrae) but a shorter thoracic (−1 vertebra) and sometimes sacral (−1 vertebra) region.

The hominoids deviate from the generalised primate pattern in some other ways.

In the cervical region, the dorsal processes are very large, especially in the largest individuals (male gorillas and orang-utans), with the seventh being the longest, as in humans.

In contrast to non-hominoid primates, the volume increase from cranial to caudal in the thoracic and (especially) lumbar region is mostly due to widening but not lengthening of the vertebrae. This is often regarded as an adaptation to the more frequent use of upright (orthograde) postures and is associated also with a broad thorax.

The lumbar articulation with the sacrum is strongly enlarged, especially in humans (Fig. 2.3).

Non-human primates, including apes, have relatively straight vertebral columns, with typically very moderate lumbar lordosis and thoracic kyphosis compared to the situation in adult humans, as seen in our closest relatives, chimpanzees (*Pan*). However, it should be noted that the spine can show some lordosis and a long lumbar region, as seen in, for example, macaques [13].

2.4 The Hominin Spine

The previous section dealt with extant species; now we will focus on extinct hominins (humans and their direct ancestors) in an attempt to illustrate how the typically human spine anatomy evolved within our lineage. The fossil record of the human spine is, however, very scarce and fragmentary. We have vertebral fossils for five Plio-Pleistocene hominins, excluding the relatively recent and in the framework of spine evolution, less interesting species such as *H. neanderthalensis* and *H. sapiens*. Out of the five species, *Australopithecus africanus* and *Homo erectus*, and recently *Australopithecus sediba*, are best documented and have adequately preserved detail [5], although for all of these species, we lack a complete vertebral column.

All fossil vertebrae for Plio-Pleistocene hominins we know have relatively long (compared to modern humans) spinal and transverse processes.

Australopithecus afarensis (approx. 4–3 million years ago, mya) is a key species for our understanding of hominin evolution in general. Fifteen vertebral elements are known for the AL 288-1 subject 'Lucy' and nine for the AL 333 sample 'the first family'. They show long cervical

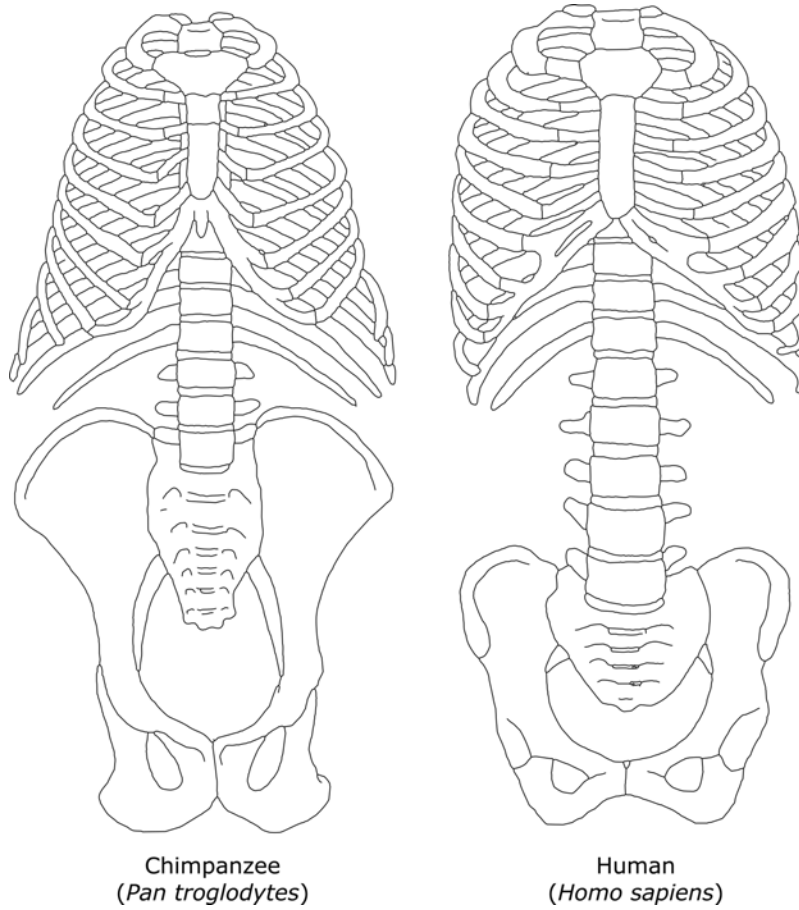


Fig. 2.3 Schematic drawing of the vertebral column, rib cage and pelvis in a chimpanzee and a human (frontal view). Note the higher pelvis, shorter lumbar region and narrow gap between the rib cage and the iliac crests in the chimpanzee as compared to the human (After Schultz [10])

and probably also upper thoracic spinous processes, which have been suggested that the erector spinae, rhomboids and trapezius muscles were particularly well developed [14].

Australopithecus africanus (approx. 3–2 mya) vertebral fossils are from Sts 14 (15 elements) and Stw 431 (12 elements) [15] subjects, plus one each for Sts 65 and Sts 73. The species possessed very long transverse processes (Fig. 2.4) in the lumbar region (esp. L3) and L3 and L4 very upwardly curved [16]. Sts 14 had five lumbar vertebrae [15].

Paranthropus fossil vertebrae number only three, from Swartkrans in South Africa (SK 3981b; [17], approx. 1.9 mya), and they are in poor state. As in *Australopithecus*, they also possess long processes. The last lumbar vertebra has transverse processes, which are up curved (as in *Australopithecus africanus*) but very long compared to both *Australopithecus africanus* and modern humans; however, *Paranthropus* is considered not to be a direct ancestor to the latter.

Homo erectus vertebrae are best known from KNM-WT 15000 'Turkana boy' (approx. 1.5 mya), and the sample consists of 14 presacral vertebrae. Haeusler et al. [18] describe the spine as an overall rather modern human-like structure, with five lumbar vertebrae and a human-like mobility and capacity for lordosis (notably, with even stronger lumbar wedging than in modern humans and in australopithecines).

Australopithecus sediba (approx. 2.0 mya) vertebral fossils have been recently described for

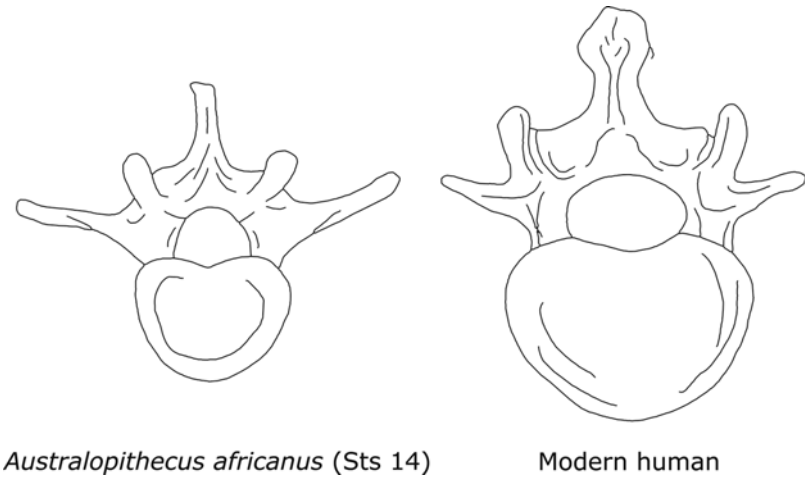


Fig. 2.4 Schematic drawing of the second lumbar vertebra (L2) in an axial view for an australopithecine and a modern human (After Robinson [16])

two individuals: MH1 (a juvenile male) and MH 2 (an adult female) [19]. They show very strong lumbar wedging (and thus lordosis), comparable to *Homo erectus*.

The picture of hominin vertebral evolution is still quite fragmentary, but some features are seen in all hominins for which sufficient fossils are available: lordosis [20–22], a pyramidal configuration of articular facets with descent through the lower lumbar column, and a wide curved sacrum. In some species (but not in *Australopithecus afarensis* and *Australopithecus africanus*), a large relative lumbosacral body size is observed [19]. Overall, key features linked to habitual bipedalism, detailed below, can be seen in all fossil hominins.

2.5 The Human Spine: Characteristics and Function

We have described the basic anatomy of the human spine, how it has evolved, and outlined some unique features in humans. In this final section, we will try to relate some of the most striking features to function. This is not always straightforward, since anatomy is not exclusively determined by function but also by evolutionary constraints. Even the functional requirements are multiple, and especially the requirement for a large birth canal in humans strongly dictates pelvic shape and, secondarily, spinal architecture (see 'spinal curvature'). However, in the case of the human spine, there is a very large consensus that habitual upright locomotion is the major driver (in evolutionary and developmental terms) and that the requirements of stability and mobility are both important (and potentially conflicting).

2.5.1 Spinal Curvature

For efficient, straight-legged, upright locomotion as seen in humans, the trunk needs to be fully erect with its centre of mass directly above the base of support. This is achieved in two ways. Firstly, by having ischio-iliac lordosis (which is outside the scope of this chapter, but see [23]) and, secondly, by having lumbar lordosis (Fig. 2.5).

Lumbar lordosis (a forward-facing convexity) in humans is, for a great part, a phenotypically plastic feature that develops as a result of upright walking. This is shown, firstly, because it is not seen in babies. Prior to the ability to walk, all sections of the vertebral column show a dorsal convex curvature [24], and it is also not seen in permanent bed-bound adults. Secondly, non-human primates can develop human-like spinal curvature during development, as seen, for example, in Japanese monkeys trained for bipedal walking (although the lordosis is largely the result of the intervertebral disk rather than the result of vertebral wedging; e.g. see [25].

Apart from pronounced lumbar lordosis, the human spine displays thoracic kyphosis (backward-facing convexity), as well as cervical lordosis and sacral kyphosis. The combined

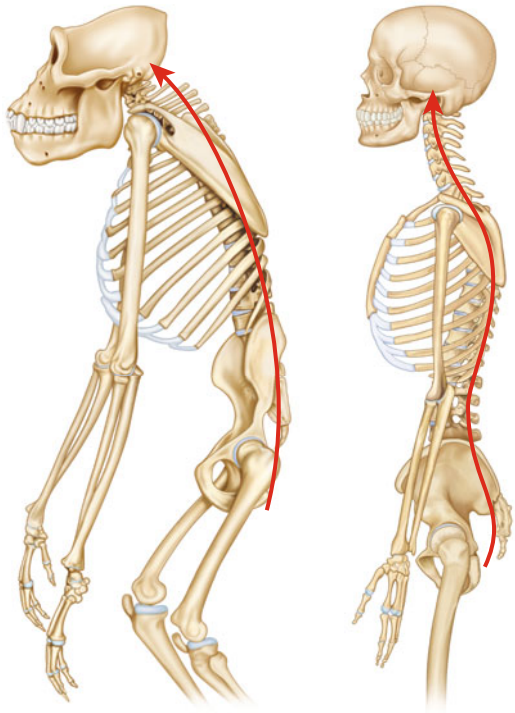


Fig. 2.5 Note the lumbar lordosis in humans (*right figure*), necessary to keep upright position of the spine, as compared to the general kyphosis of the spine in hominoids (*left figure*)

curvature of the spine also helps (with the intervertebral disks) to absorb shocks. Interestingly, an average lumbar lordosis is women seems to be most attractive in men (see Chap. 39).

Anatomically, lumbar lordosis is a result of dorsal wedging in L4 and L5 (in males) and L3–L5 (in females, [26]) and of the deformable, intervertebral disks. Furthermore, these disks are higher ventrally than dorsally. This is an important finding when considering lumbar spine reconstruction.

2.5.2 Spinal Mobility

The second fundamental difference between the ape and the human spine lies in its overall increased mobility. This is a result of mobility of the spine itself, combined with the shape of the rib cage and the pelvis, which are also very different in humans and apes.

The increased mobility in humans is caused by the increased number of lumbar vertebra, outlined higher, but further enhanced by a number of other features. The pelvis of great apes is much higher than that of humans, and the iliac blades virtually enclose the lowest lumbar vertebrae. This iliac structure combined with the extended rib cage (which further reduces flexion and extension movements in the thorax) also means that the gap between these is very small, sometimes only a few centimetres (Fig. 2.3). This further limits overall trunk mobility in apes but not in humans, where the lumbar region is the most mobile one, after the cervical region. Since all the great apes, with which we share a common ancestor, had such a stiff trunk (suited for arboreal locomotion), it has been argued that hominins started with a similarly short trunk; however, it has also been proposed that they did not and that the short lumbar regions of apes have evolved independently from a longer primitive primate lumbar region [11].

Motion is also to a great extent explained by articular processes. Humans have relatively short transverse and spinous processes (the latter angles downwards more steeply than in apes), which provides shorter leverage for the muscles but enhances mobility. Moreover, the surfaces of the articular processes are oriented in order to allow movement, being curved and sagittally oriented in the lumbar region, allowing for flexion and extension, but flat and coronally oriented in the thoracic region, allowing primarily lateral bending and rotation, but much less flexion and extension.

2.5.3 A Strong Lumbosacral Region

Lumbar vertebrae increase in size caudally; in humans (but not in apes) the left-to-right distance between the facets of the paired articular processes (which are, moreover, very well developed) also increases [8]. This is necessary for the articulation with the wide sacrum (see below). At lumbosacral joint, the inferior facet joints are reoriented to prevent the entire spine sliding off the highly angled sacrum (further helped by the enlarged sacrospinous ligament).

The human sacrum is absolutely and relatively enlarged (notably in width) compared to the ape sacrum; it is more curved and has a larger articulation (the auricular surface) with the pelvis. Compared to apes, humans display less partial sacralisation of lumbar vertebrae [9].

Human bipedal walking requires both an increased stability (due to the important loads involved) and an increased mobility. These are conflicting demands, which (with some other, notably obstetric factors) have shaped the human spine throughout the course of hominin evolution. This has led to a compromise anatomy (see Putz et al. [27]), which together with the relatively poorly developed erector spinae might help explain the predisposition for lower back injuries in humans [28].

References

1. Kardong K (2012) Vertebrates: comparative anatomy, function, evolution. McGraw-Hill, New York
2. Galis F (1999) Why do almost all mammals have seven cervical vertebrae? Developmental constraints, Hox genes, and cancer. J Exp Zool 285:19–26
3. Fleagle J (2013) Primate adaptation and evolution, 3rd edn. Academic Press, San Diego
4. Ankel-Simons F (2007) Primate anatomy, 3rd edn, An introduction. Academic Press, San Diego
5. Williams SA (2012) Placement of the diaphragmatic vertebra in catarrhines: implications for the evolution of dorsostability in hominoids and bipedalism in hominins. Am J Phys Anthropol 148:111–122
6. Haeusler M, Martelli SA, Boeni T (2002) Vertebrae numbers of the early hominid lumbar spine. J Hum Evol 43:621–643
7. Rose M (1975) Functional proportions of primate lumbar vertebral bodies. J Hum Evol 4:21–38
8. Aiello L, Dean C (1990) An introduction to human evolutionary anatomy. Academic, London
9. Abitbol MM (1987) Evolution of the sacrum in hominoids. Am J Phys Anthropol 74:65–81
10. Schultz A (1961) Vertebral column and thorax. In: Schultz A (ed) Primatologia. Karger, Basel, pp 1–66
11. McCollum MA, Rosenman BA, Suwa G, Meindl RS, Lovejoy CO (2010) The vertebral formula of the last common ancestor of African apes and humans. J Exp Zool B Mol Dev Evol 314:123–134
12. Williams S (2011) Evolution of the hominoid vertebral column. University of Illinois, Urbana
13. Le Gros Clark W (1962) The antecedents of man. University of Edinburgh Press, Edinburgh
14. Cook DC, Buikstra JE, DeRousseau CJ, Johanson DC (1983) Vertebral pathology in the afar australopithecines. Am J Phys Anthropol 60:83–101
15. Toussaint M, Macho G, Tobias P, Partridge T, Hughes A (2003) The third partial skeleton of a late pliocene hominin (stw 431) from Sterkfontein, South Africa. South Afr J Sci 99:215–223
16. Robinson J (1972) Early hominid posture and locomotion. University of Chicago Press, Chicago
17. Susman R (1988) New postcranial remains from swartkrans and their bearing on the functional morphology and behavior of paranthropus robustus. In: Grine F (ed) Evolutionary history of the "robust" " australopithecines". Aldine de Gruyter, New York, pp 149–172
18. Haeusler M, Schiess R, Boeni T (2011) New vertebral and rib material point to modern bauplan of the Nariokotome Homo erectus skeleton. J Hum Evol 61:575–582
19. Williams SA, Ostrofsky KR, Frater N, Churchill SE, Schmid P, Berger LR (2013) The vertebral column of Australopithecus sediba. Science 340:1232996
20. Been E, Barash A, Marom A, Kramer PA (2010) Vertebral bodies or discs: which contributes more to human-like lumbar lordosis? Clin Orthop Relat Res 468:1822–1829
21. Been E, Gomez-Olivencia A, Kramer PA (2012) Lumbar lordosis of extinct hominins. Am J Phys Anthropol 147:64–77
22. Been E, Gomez-Olivencia A, Kramer PA (2014) Brief communication: lumbar lordosis in extinct hominins: implications of the pelvic incidence. Am J Phys Anthropol 154:307–314
23. Schlosser TP, Janssen MM, Vrtovec T, Pernus F, Oner FC, Viergever MA, Vincken KL, Castelein RM (2014) Evolution of the ischio-iliac lordosis during natural growth and its relation with the pelvic incidence. Eur Spine J 23:1433–1441
24. Paulsen F, Waschke J (2013) Sobotta atlas of human anatomy, vol 1, 15th edn, General anatomy and musculoskeletal system (english version with english nomenclature). Elsevier, Urban & Fischer Verlag, München
25. Hirasaki E, Ogihara N, Hamada Y, Kumakura H, Nakatsukasa M (2004) Do highly trained monkeys walk like humans? A kinematic study of bipedal locomotion in bipedally trained Japanese macaques. J Hum Evol 46:739–750
26. Whitcome KK, Shapiro LJ, Lieberman DE (2007) Fetal load and the evolution of lumbar lordosis in bipedal hominins. Nature 450:1075–1078
27. Putz RL, Muller-Gerbl M (1996) The vertebral column – a phylogenetic failure? A theory explaining the function and vulnerability of the human spine. Clin Anat 9:205–212
28. Lovejoy CO (2005) The natural history of human gait and posture. Part 1. Spine and pelvis. Gait Posture 21:95–112

Cell Regeneration: Current Knowledge and Evolutions

3

Jasper Van Hoorick, Hugo Thienpont, Peter Dubruel, and Sandra Van Vlierberghe

Contents

J. Van Hoorick, MSc • S. Van Vlierberghe, PhD (✉)
Department of Polymer Chemistry and Biomaterials Research Group (PBM-Ugent), University of Ghent, Ghent, Belgium

Department of Brussels-Photonics Research Group (B-PHOT), University of Brussels, Brussels, Belgium
e-mail: sandra.vanvlierberghe@ugent.be, svvlierb@bphot.org

P. Dubruel, PhD
Department of Polymer Chemistry and Biomaterials Research Group (PBM-Ugent), University of Ghent, Ghent, Belgium

H. Thienpont, Ir, PhD
Department of Brussels-Photonics Research Group (B-PHOT), University of Brussels, Brussels, Belgium

3.1 Introduction

3.1.1 Problem Statement

Low back pain is one of the most common complaints throughout the modern western society [1–5]. It can lead to a chronic disability for 10 % of the patients resulting in a huge economic burden for society and often an incapacitating life for the patient. As low back pain often goes concomitant with intervertebral disk (IVD) degeneration [3, 4, 6], tissue engineering solutions for IVD gained increasing attention during the last decade.

The spinal column is one of the largest components of the human skeleton. It serves a dual role as it provides trunk flexibility while supporting the upper body weight [7, 8]. In addition, it has to function as an armor for the spinal cord and the nerve roots that pass through [9]. In humans, the spine is composed of 33 stacked vertebrae, most of which sandwich an IVD. Twenty-four of these

E. Van de Kelft (ed.), *Surgery of the Spine and Spinal Cord. A Neurosurgical Approach*.
DOI 10.1007/978-3-319-27613-7_3

vertebrae form a flexible part, while nine vertebrae form a rigid part inside the pelvis [7].

The IVDs act as a joint between the separate spinal column vertebral bodies. They are supported in this task by two zygapophyseal joints (facet joints) located at the backside of the spinal column and forming a three-joint complex [10]. This three-joint complex is responsible for the flexibility and load transmission throughout the spine [5]. When the IVDs degenerate, they lose height, which can affect the entire spinal column resulting in back pain and/or a loss of spinal mobility and/or development of segmental instability. In the long term, major instability and subsequently spinal stenosis, which is the main cause of neurogenic claudication for the elderly, can ensue [2]. This chapter will mainly deal with the pathophysiology of the (lumbar) disk and the theoretical tissue engineering solutions.

The cause of IVD degeneration is not fully defined, yet it is anticipated to be the result of a combination of factors including natural aging, mechanical compression, genetic factors, inadequate metabolite transport, altered levels of enzyme activity, smoking, load history, etc. [4, 5, 11–17]. IVD degeneration typically occurs in an earlier stage when compared to the degeneration of other musculoskeletal tissues. The first signs of degeneration can already be observed in about 20 % of youngsters aging from 11 to 16 years old [2, 6].

3.2 Anatomy and Physiology of the Intervertebral Disk

3.2.1 Anatomy of the Intervertebral Disks

An IVD is a rather avascular system [8], consisting of three main regions including the nucleus pulposus (NP), the annulus fibrosus (AF), and the cartilaginous end plates [2] (Fig. 3.1, left).

The NP is the gelatinous core of the IVD [3], with the major component being water (65–85 % of its total weight) [2, 5, 18]. It contains randomly organized collagen fibers and radially aligned elastin fibers embedded in a highly hydrated proteoglycan (PG) gel. The main PG present is aggrecan, which generates an osmotic pressure. This pressure originates from the presence of chondroitin sulfate and keratan sulfate chains which are responsible for hydration [2, 11, 14]. In addition, the NP consists of a low density of chondrocyte-like cells embedded in a disorganized matrix mainly consisting of type II collagen fibers. It shows fluid-like behavior yet acts as an elastic solid upon mechanical loading [19]. The shear modulus G* ranges from 7 to 21 kPa [20], while its compressive elastic modulus varies between 3 and 15 kPa [21].

The AF is more fibrous-like and consists of 15–20 concentric lamellae. These lamellae contain parallel-aligned collagen fibers, primarily

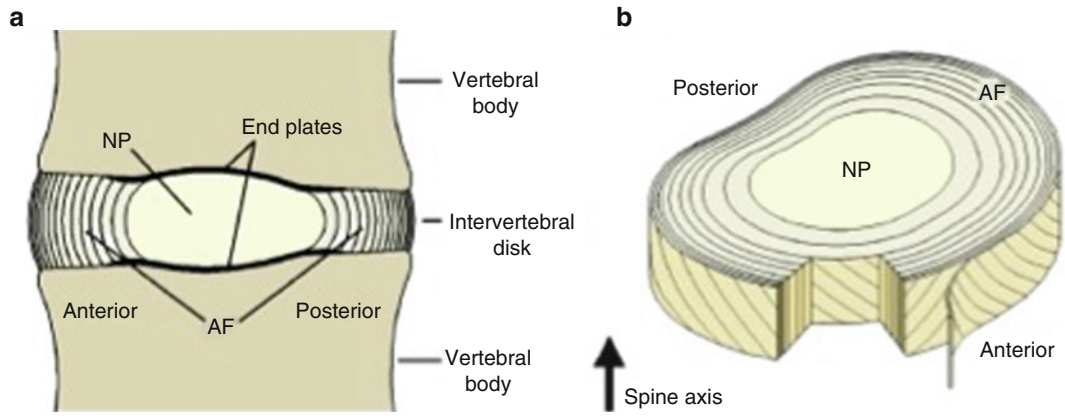


Fig. 3.1 Schematic overview of the anatomy of the intervertebral disk with its characteristic regions (Reprinted with permission from [13]). Note that in the lumbar spine especially, the height of the anterior AF exceeds the one of the posterior AF, creating the lumbar lordosis

type I, which are oriented at an angle of 62° relative to the spinal axis at the edges of the AF. The center of the AF mainly consists of collagen type II fibers oriented at an angle of about 45° relative to the spinal axis [3, 7, 18, 22]. The angle of the fibers of one lamella layer is rotated over 180° in comparison to the fibers of the previous layer (Fig. 3.1) [19]. Furthermore, the AF contains proteoglycans and elastin fibers which connect the different lamellae thereby generating a high axial strength [22]. In addition to collagen and elastin fibers, the AF contains elongated, fibroblast-like cells which are aligned parallel with the collagen fibers [2, 14]. The cells maintain the complex extracellular matrix (ECM) structure to preserve the biomechanical properties of the AF [5]. The AF is characterized by a shear modulus G* of 540 kPa [23].

Finally, the cartilaginous end plates are thin horizontal layers consisting of an outer osseous component and an inner hyaline cartilage region [8]. The central region consists of a hydrated PG gel which is reinforced by collagen fibrils [8]. It enables diffusion of nutrients and waste to and away from the disk [19]. The end plates act as an interface between the IVD and the vertebral body and prevent the NP from bulging into the vertebral body [8]. Similar to the other IVD components, they mainly consist of collagen fibers aligned parallel with the vertebral bodies [2]. The end plates are characterized by a shear modulus G* of 440 kPa [23].

Collagen is the major component of the IVD as it accounts for 90 % of its dry weight. It serves important mechanical properties as it absorbs water. This protein, alongside the PGs, creates a swelling pressure, which is large enough to maintain a distance between the loaded vertebrae. Compressive loads are supported mostly by pressurization of the NP, in combination with the minimal hydraulic permeability of the AF, which prevents the NP to burst. The bending and shear stresses on the spine are borne mostly by the mechanically robust AF [5]. In addition, the collagen fibers inside the end plates serve an anchoring function for the IVD to the vertebral bones [2].

Various interesting features can be distinguished when considering IVD tissue:

- Firstly, the presence of long, thin cytoplasmic cell projections can be observed, which are typically absent in cells of any other articular cartilage. It can be anticipated that they serve as sensors and communication devices for mechanical strain within the tissue [2].
- Secondly, in the native not degenerated disk, there is an almost complete absence of blood vessels and nerves. If present, they are only observed in the outer lamellae [2, 8]. This feature causes a poor nutrient supply throughout the IVD. This leads to poor regeneration capacities as the cells are completely dependent on passive diffusion of nutrients through the end plates and subsequently the extracellular matrix (ECM) [11, 24]. The nutrient transport is consequently very dependent on the composition of the ECM [2].
- Finally, the IVD contains a higher amount of PG compared to articular cartilage.

3.2.2 Pathophysiology of the Intervertebral Disk

Degenerative disk disease (DDD) has significant consequences on the three parts of the IVD. However, since this degeneration occurs in every individual and no correlation exists between the degree of disk degeneration and symptoms, the word “disease” does not seem to be appropriate for this normal degeneration process. During skeletal maturation, the boundaries between the NP and the AF start to fade and the NP loses some of its elasticity as it becomes gradually more fibrotic and less gel-like [27, 28]. The latter results in a drastic reduction of the biomechanical properties of the IVD [3]. Another important aspect in DDD is an increase in endplate calcification and associated decrease in nutrient transfer to the IVD [29].

The origin of these phenomena can be traced back to a series of changes occurring inside the IVD. At an early age, notochordal cells are present in IVDs [12, 13] (see also Chap. 1). Interestingly, these cells can generate large amounts of ECM. However, upon maturation, these cells gradually disappear, thereby reducing

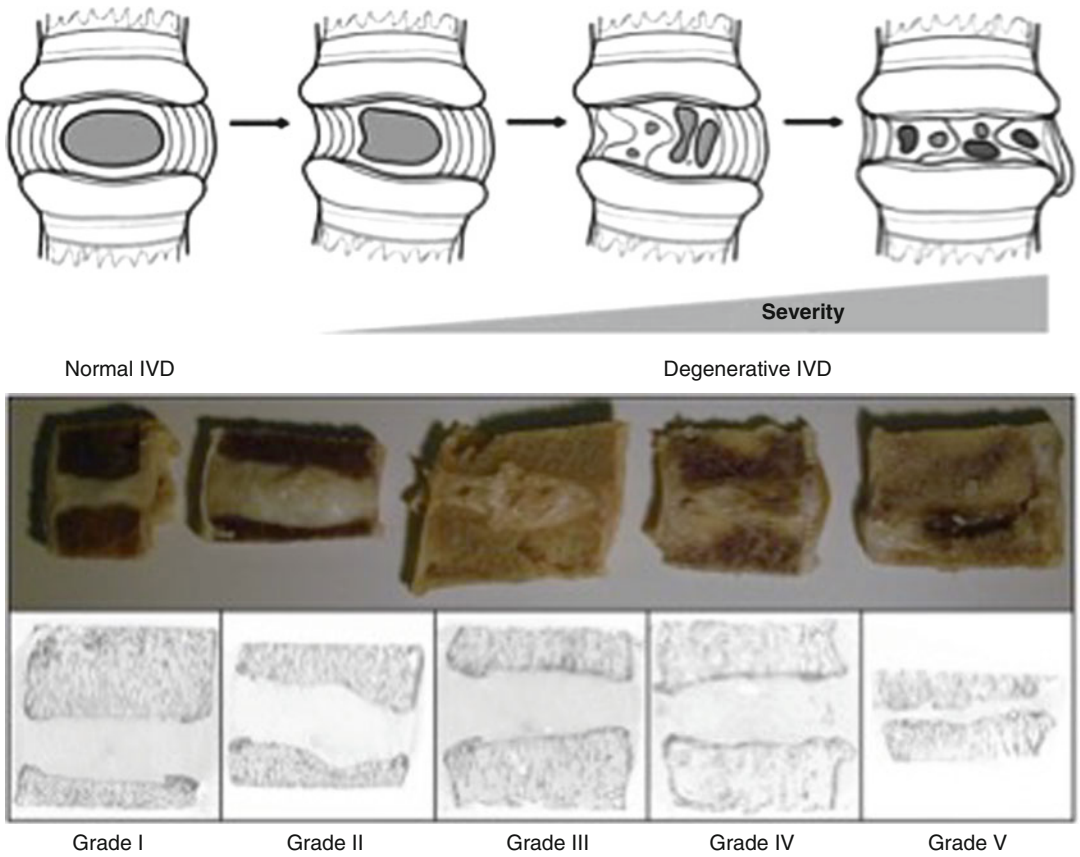


Fig. 3.2 (*Top*) Overview of several stages occurring during IVD degeneration: (1) healthy disk; (2) depressurized NP, NP repressurization/replacement necessary; (3) AF disruption, AF replacement necessary; (4) both NP and AF are degraded, end plates have calcified, and severe loss in disk height, full IVD replacement required (Reprinted from Chan et al. [25] with permission from Elsevier). (*Bottom*) Macroscopical appearance and micro-CT images of IVDs in several stages of degeneration (Reprinted from Rutges JPHJ et al. [26] with permission from Elsevier)

ECM (re)generation [14]. In addition, enzymatic breakdown of the proteoglycans results in a reduction of hydration in the NP [14]. The endplate calcification, in combination with a reduced blood supply during early childhood, reduces nutrient flow to the NP and the AF which results in necrosis of the ECM synthesizing chondrocytes [14]. The abovementioned processes give rise to a decreased ECM regeneration. As a result, the PG degradation is further accelerated [2, 29–31]. Finally, a drop in type II collagen content is observed, while an increase in type I collagen is observed inside the NP [20, 30].

The degradation of IVDs can result in several types of IVD failure including the occurrence of tears in the AF which can result in bulging (the outer layers of the AF remain intact; however, as a consequence of damage to the inner layers, the NP will exert pressure on the weakened AF and bulging of the IVD ensues), herniation (the outer layers of the AF are not intact anymore; upon pressure, the NP will partially protrude or extrude) (see also Chap. 21), and loss of disk height (chemical changes inside the NP cause it to dry out. The associated drop in hydraulic pressure results in a thinning of the disk) [5] (Figs. 3.2 and 3.3).

The loss in water content due to a reduction of the PG present in the NP reduces the ability to maintain osmotic pressure upon mechanical load. The latter further increases the loss of fluid and the stress exerted on the AF leading to compression of the IVD. In addition, a reduction in NP pressure hampers proteoglycan synthesis, which

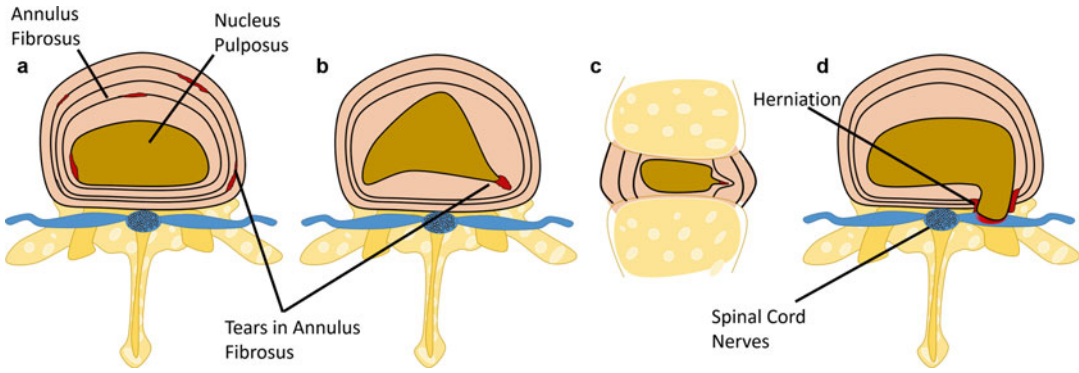


Fig. 3.3 Most common types of annulus tears: concentric tears or AF delamination (**a**). Radial tears (**b**, **c**) without complete disruption of the AF (**d**). Image (**b**) and (**c**) depict bulging of the IVD as a consequence of radial tears in the AF; image D depicts IVD herniation which exerts pressure on the spinal nerves

results in a further reduction of hydration and, consequently, the inability to auto-repair the damaged tissue [32]. Moreover, a height reduction in one IVD generates increased levels of stress on other parts of the spine, resulting in a synergistic effect of spinal complications (cfr. adjacent level disease after arthrodesis surgery) [2]. These spinal complications can include, among other, degenerative effects on other IVDs as well as on the lumbar zygapophyseal joints (facet joints) [33]. These joints also serve a load-bearing function (especially in the cervical spine) and partially take over this function from the degenerated IVD. In the presence of a healthy IVD, they support up to 33 % of the compressive forces, while this number can go up to 70 % in the presence of a degenerated IVD [33]. Consequently, an increase in density of the subchondral facet joint bone is observed alongside osteophyte formation [34]. This process can induce a cascade of problems related to the spinal system including full-thickness cartilage necrosis, ulceration, fibrillation, eburnation, abnormal joint motion, bony hypertrophy, and, finally, spinal stenosis and/or major segmental instability [33]. Spinal stenosis may be the result of facet joint osteophyte formation, disk herniation, yellow ligament hypertrophy, segmental instability, and changes in the spinal contour [10]. Furthermore, the presence of aggrecan, the main PG present, prevents vascular and neural ingrowth [35, 36]. As a result, the degradation of PGs gives rise to an increase of vascular and neural ingrowth, which is anticipated to be an attempt of the body to increase nutrient supply in order to restore the IVD [8, 37]. However, the presence of nociceptive nerves in a load-bearing system causes additional initially nociceptive back pain as these nerves experience compressive forces [2, 14, 38, 39] (see also Chap. 22).

Another important aspect of DDD is the reduced organization of the collagen fibers inside the AF, which affects the biomechanical properties to a great extent [2]. The drop in biomechanical properties of the AF can result in the formation of concentric tears (cfr. disk delaminations) and radial tears upon load [2, 14, 40] (Fig. 3.3). Through these tears, the NP can (partially) influence the contours of the AF, leading to bulges and disk herniation (protrusion/extrusion) [30], resulting in acute and chronic pain as a consequence of the exerted pressure on adjacent nerves [2, 41].

Finally, end-plate damage can cause the NP to herniate into the end plate. As a consequence, the AF can collapse into the NP area upon mechanical load as a result of the reduced NP pressure [14].

3.3 Conventional Clinical Therapies

Current conservative treatments for low back pain associated with IVD degeneration are aiming at reducing discomfort and treating the symptoms rather than repairing the mechanical function of the IVD [2, 3]. They typically do not address the loss of disk height nor the mechanical functions associated with IVD degeneration [3, 13]. They can even

further induce the degeneration due to alterations in biomechanics [3] which result in a necessity for additional surgical interventions [42].

The first set of treatments are conventional, noninvasive techniques consisting of oral analgesics, nonsteroidal anti-inflammatory drugs, and physical therapies. However, these treatments tend to focus more on pain relief rather than addressing the cause of the problem. Furthermore, it typically takes months before "satisfactory" results are obtained, and no evidence exists that these treatments are beneficial [2].

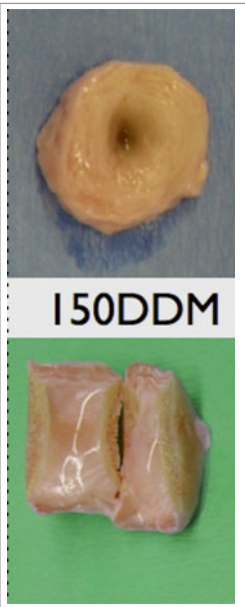
Secondly, some minimally invasive techniques aim at reducing the pressure exerted on the nerves which is caused by bulging and herniation of the disk. These techniques are referred to as nucleotomy, (micro)diskectomy, and annuloplasty and imply that part of the IVD, generally part of the NP, is removed to reduce the pressure exerted on the nerves [2, 30, 38, 43]. Although instant pain relief can be observed in the short term, these techniques can lose their benefits because of the poor regeneration properties of the IVD and the possible occurrence of additional degeneration during longer timeframes [22].

Alternatively to these minimally invasive treatments, there are two major invasive approaches to treat intervertebral defects [42]. First, spinal arthrodesis [19] can be carried out in order to fuse two or more adjacent vertebral bodies around the damaged IVD(s). The ultimate goal of this surgery is to become a bony fusion. Therefore, this type of intervention should be called "arthrodesis" (literally the fixation of a joint) rather than "fusion" surgery. Fusion is, in the optimal condition, the result of arthrodesis. Furthermore, it is not so easy to demonstrate fusion, and fusion is not associated with a good postoperative result as nonunion is not associated with a bad postoperative result. Although this technique is currently considered as the standard treatment for degenerative disk disease, there is no evidence that it is in the long term more beneficial than conservative treatment (see also Chaps. 23 and 24) [9]. It increases stress on areas surrounding the spinal column which can lead to additional problems as stated above; adjacent segment disease does exists [34, 44]. A second technique includes a complete surgical removal of the traumatized IVD and its replacement by an artificial one or arthroplasty, referred to as total disk replacement (TDR) [4, 9, 32, 43–47]. This technique has emerged as an alternative for spinal fusion to address a possible loss of biomechanical properties. The postoperative results can be compared with the ones after fusion. In the cervical spine, the postoperative results even look better than after cervical arthrodesis. Recently, progress has already been realized in this field by applying rapid manufacturing/prototyping (commonly referred to as 3D printing) as a tool to construct patient-specific implants [48]. Although this technique offers some theoretical benefits over spinal fusion, it still exhibits significant drawbacks including a limited biocompatibility (depending on the material applied), inconsistent mechanical behavior which induces additional stress on the column [45], a poor fixation which could lead to subluxation of the implant or the opposite, fusion [46, 49], and the production of wear debris (often polyethylene (PE)) upon repetitive mechanical loads which can induce inflammatory responses (see Table 3.1) [5, 22, 47, 49–51].

3.4 Tissue Engineering Treatments

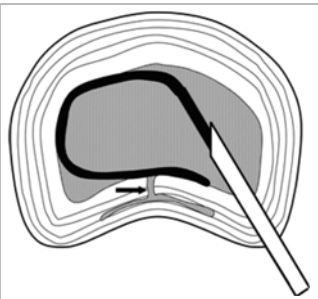
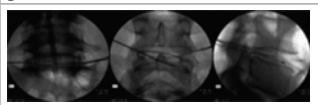
Tissue engineering is a scientific research field, which aims at the development of novel technologies to address the numerous challenges faced when dealing with tissue repair. On the one hand, it aims at suitable alternatives for conventional organ transplants and all of its associated hurdles. On the other hand, alternative treatments are also targeted for currently unsatisfying treatments including IVD degeneration [64]. Today, no evidence exists that these treatment options yield better long-term results than seen during the natural history of IVD or after its conservative treatment. A promising approach however, in this respect, is the use of biomaterials as starting compounds for functional scaffolds. Ideally, the scaffolds developed should closely resemble the natural ECM while showing a predetermined macroscopic shape. They can be introduced at the site of a tissue defect [30] to act as a support for stem cell adhesion, differentiation, and

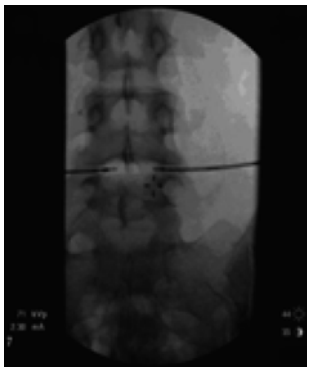
Table 3.1 Overview of (pre)clinically applied IVD degeneration treatments

Methodology	Description	Benefits	Drawbacks	Illustration
Treatments for IVD degeneration				
Conservative treatment	A combination of oral analgesics, exercise, cognitive reconditioning and physiotherapy [2]	*Noninvasive *No revalidation EBM *NSAIDs: B [52] *Exercise: B [53] *Physiotherapy: B [54]	*Symptomatic treatment *It takes months to obtain "satisfactory" results *Demanding for the patient	
Minimally invasive procedures				
Nucleolysis				
Chemonucleolysis	*Treatment of herniated IVD *Chymopapain injected directly in NP, dissolves proteoglycans, shrinks bulging disk, leaves AF intact [2, 43, 55]	*Back pain is diminished instantly *Minimally invasive procedure *EBM: B [56]	*Complications (anaphylaxis) *Healing after nucleotomy is observed by formation of vascular tissue through ruptures in the bony end plates and can cause pain	 Degeneration of NP in disks 10 days after injection with papain at 115U/ml. Top and side view of the IVD.(Reprinted from [43] with permission from Elsevier)

(continued)

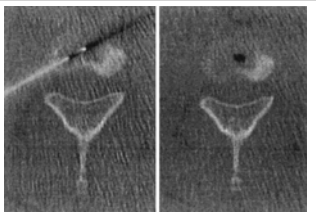
Table 3.1 (continued)

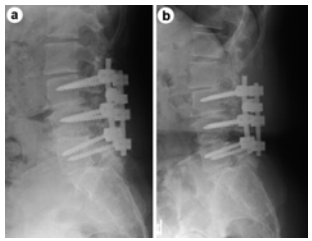
Methodology	Description	Benefits	Drawbacks	Illustration
Ozone chemonucleolysis	*Treatment of herniated IVD *Injection of ozone/oxygen mixture into paravertebral musculature and in the herniated zone [2]	*Painless *Well tolerated	*Insufficient published data to show the effects of treatment *No EBM	
Annuloplasty				
IDET (intradiskal electrothermal therapy)	*Treatment for chronic diskogenic lower back pain *Thickens collagen, leading to a contraction and a diminishment in vascular and neural ingrowth *An electrode is inserted in the defective area and heated to 90 °C [2, 57]	*Minimally invasive *Patient is discharged on the same day *Can lead to a reduction of annular fissures *Can increase the stability of the disk itself *Low cost	*Limited amount of long-term results available *Thermocoagulation of the nociceptors within the annular walls can occur *Possible complications: catheter breakage, post IDET disk herniation, infection, abscess, neuronal damage *Moderate evidence to prove effectiveness of the treatment *EBM: B [58]	 Schematic picture showing the introduction of the electrode into an IVD (Reprinted from [59] with permission from Elsevier)
RFA (radiofrequency annuloplasty)	*Treats patients with chronic low back pain *DiscTRODE™ cannula is inserted in outer disk tissue under X-ray guidance *Radiofrequency current flows through the electrode, locally heating the adjacent tissue and coagulating and thickening the collagen present [2]	*Minimally invasive *Low cost *Few side effects compared to surgical options	*Complications: catheter breakage, nerve root injuries, diskitis, disk herniation, epidural abscess, spinal cord damage at thoracic and cervical regions *Only short-term evidence for benefits *EBM: B [58] short term	 X-ray image representing the placement of the heating catheter and thermocouple to monitor the temperature increase (Reprinted from [60] with permission from Elsevier)

IDB (intradiskal biacuplasty)	*New annuloplasty procedure *Bipolar system of two RF electrodes is used *Electrodes are placed on opposite posterolateral sides of the defective annulus fibrosus [2, 38]	*Minimally invasive *Lower peak temperature compared to IDET leads to better tolerance *Short procedure *Can be used in previously operated disks *Relative ease for placement of electrodes compared to RFA and IDET	*Insufficient long-term data on long-term effects *No EBM [58]	 X-ray image showing the placement of both electrodes (© 2009 World Institute of Pain Reprinted from [38] with kind permission from John Wiley and Sons)
Percutaneous disk decompression				
Laser diskectomy	*Patients with herniated IVD *A laser is inserted under fluoroscopy into the NP *Laser irradiation, removes small portions of the NP, enabling the herniation to shrink [2, 61]	*Minimally invasive *Patients can return home the same day *Very localized tissue removal *Can be applied on patients with spinal stenosis and IDD (intervertebral disk disruption)	*Scarcity of clinical trials *Steep learning curve for the surgeon *Increases difficulty level for surgeon *Moderate evidence for success *No EBM [43]	

(continued)

Table 3.1 (continued)

Methodology	Description	Benefits	Drawbacks	Illustration
RF coblation (plasma diskectomy)	*Patients with herniated IVD *The device is entered into the NP through a needle guided by fluoroscopy *NP is ablated with RF when introducing the device *Tissue is transferred to gas by molecular dissociation, which is then aspirated through the needle *After removal of the device, coagulation takes place by thermal treatment of the canal which leads to a denaturation of nerve fibers [2]	*Minimally invasive	*Not applicable to patients with spinal stenosis *Loss of disk height of 50 %, severe disk degeneration *Moderate evidence of success *No EBM [56]	 CT image of placement of the device inside the IVD (left) before and (right) after coblation (Reprinted from [62] with permission from Elsevier)
Mechanical disk decompression A probe is inserted, slicing manual PLD (percutaneous lumbar diskectomies)	*Dekompressor is a handheld device, connected to a helical probe, the probe rotates thus sucking out milled tissue from the NP *The Dekompressor is placed into the IVD under fluoroscopic guidance [2]	* Minimally invasive *Short surgical procedure times	*Results on this procedure are still limited *Moderate evidence of success *EBM: D [63]	 Picture of the handheld device (Reprinted from [64] with permission from Elsevier)
	*A probe is inserted, slicing tissue in the IVD, which is subsequently aspirated [2]	*Minimally invasive *Relatively short surgical procedure times	*Varying results *EBM: B [56]	
Regional endoscopic techniques				
Lumbar diskectomy	*Using an endoscope inserted through working tubes, very local pieces of the prolapsed disk can be removed under direct (or video) vision [2]	*Ultimate form of minimally invasive spinal surgery *Patient can go home within 24 h	*No difference in clinical results on the long term with classical microdisketomy * EBM: A on the short term as compared to conservative treatment [56] *Not superior to microdiskectomy on the longer follow-up	

Major surgical procedures				
Spinal arthrodesis				
	Adjacent vertebral bodies are fixed using some kind of fixation device and application of bone [9]	*Can help in instability and loss of spinal contour	*No restoration of disk function *Adjacent level disease *Alters biomechanics of the spinal column *EBM as treatment for chronic aspecific low back pain: D [62]	 Radiographs after decompression and spinal arthrodesis after surgery (A) and after 2 years (B) (Reprinted from [63] with permission from Elsevier)
Artificial IVD replacements, total disk replacement (TDR)				
	*The diseased IVD is surgically removed and replaced by an artificial one [9, 48]	*Restoration of interbody height and some kind of motion	*Cannot sustain compressive forces *Production of wear debris *Stress transfer to vertebrae *Possibility of implant failure *Little long-term results *In the lumbar spine, not significantly better than arthrodesis in the treatment of DDD, but certainly not worse *No EBM for TDR as compared to conservative treatment for DDD	 Model of an IVD implant produced by rapid manufacturing (Reprinted from [50] with kind permission of Emerald Publishing Limited)

* bullet point, + benefits, - drawbacks

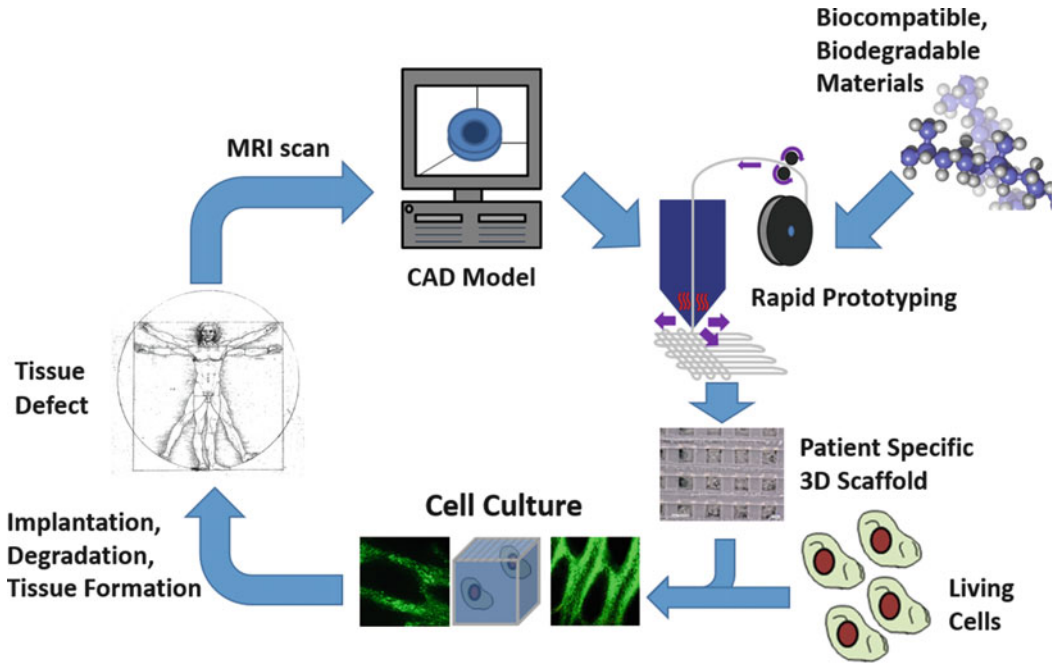


Fig. 3.4 Scheme demonstrating the principle of tissue engineering

proliferation, in order to finally result in the generation of new tissue (Fig. 3.4) [64–68].

As a result to the lack of fundamental treatment, alongside poor evidence supporting conservative as well as surgical treatments, recently, increasing attention has been paid to alternative, more sustainable treatments which focus on restoring disk height and biomechanical functions by introducing tissue engineering approaches [2, 19, 30, 69, 70].

The first aspect to engineered IVDs is the whole-organ culture [71]. The focus thereby lays on understanding the mechanisms behind IVD degeneration and the factors that enhance disk regeneration ex vivo. Several factors are studied in that respect including the effect of mechanical stresses exerted and nutrient supply on the cell viability [24], areas of the IVD which show increased or decreased cell proliferation, etc. The abovementioned studies are key to realize the regeneration of IVDs [5].

Three methods are currently under investigation for IVD regeneration including AF repair, NP repair or replacement, and total IVD replacement. The selection and the success rate of the different approaches are often depending on timing and the nature of the observed degeneration [5] (Fig. 3.2).

3.4.1 Overview of Available Cell Sources

Tissue engineering (TE) of IVD requires a high number of clinically suitable cells [3] which forms one of the main obstacles to date [3, 27, 30, 42] since even healthy IVDs and especially the NP are characterized by a low cellular density. In addition, extracting cells from healthy IVDs to repair degenerative IVDs can result in an increased degeneration of the healthy disk [27]. As successful regeneration requires more cells than can be harvested from a single IVD, different cell sources have to be addressed [3, 6, 72].

At present, different cell sources are under consideration to enable TE of IVD. Firstly, autologous chondrocytes can be obtained from non-spinal sites [27, 42], while autologous disk chondrocytes are typically harvested through a diskectomy or percutaneous biopsy [73]. The benefits of these

cells include their similarity with IVD chondrocytes [27]. Furthermore, the use of autologous cells excludes immunogenic body responses [73]. Secondly, some researchers address the use of allogeneic IVD cells (i.e., cells from a different individual), but this method raises questions concerning immunological reactions, difficulties related to cell culture and preservation, and potential disease transmission [74]. Furthermore, this procedure can cause IVD degeneration in the donor [74]. Finally, mesenchymal stem cells (MSCs) [3, 6, 11, 31, 43, 75–78] or bone marrow stromal cells (BMSCs) can be applied as they are not yet differentiated and multipotent (cfr. able to differentiate into a large variety of cell types) [11, 72]. The application of MSCs for IVD regeneration holds several advantages including [3, 11, 31]:

- Relatively easy to be harvested from bone marrow
- Straightforward in vitro culture
- Self-renewal and expansion behavior
- Low immunogenicity ruling out tissue rejection post-implantation
- Differentiation possible into a variety of cells including cell types present in the AF and the NP

Unfortunately, the application of MSCs also holds some risk as these cells exhibit the ability to transform into a large variety of cells. The latter can become troublesome upon leaking from the implant site and the formation of osteophytes [42]. The in vitro manipulation of the cells prior to the implantation (cfr. coculture with NP cells) forms a viable alternative to generate large populations of the appropriate cells to realize TE of the NP [3, 6].

3.4.2 Nucleus Pulposus Replacement

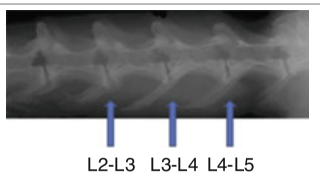
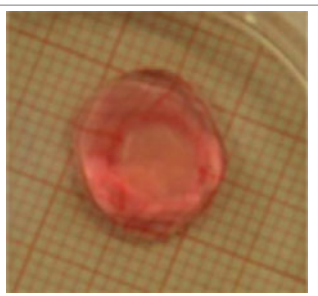
As the early symptoms of IVD degeneration can be attributed to transformations occurring inside the NP, a lot of research has been focused on augmenting or regenerating the NP [27, 42, 79, 80]. In general, the studies aim at increasing the PG content to restore the hydraulic pressure inside the NP, which is crucial for its mechanical function [5, 70]. The regeneration of the NP can be extremely useful in the early stages of DDD prior to AF degradation (Fig. 3.2) [81].

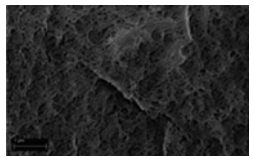
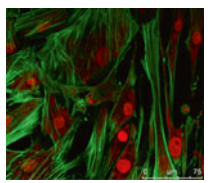
Two approaches exist to realize an increase in PG content. First, the cells present in the NP can be stimulated to upregulate their ECM production by administering growth factors such as TGF-β and BMP-2 [3, 6, 31, 68, 70]. Unfortunately, although these growth factors result in an increase of the major ECM components, collagen and glycosaminoglycans (GAGs) [6, 31, 68, 70], they can also lead to ossification of the AF [82]. Furthermore, the successful introduction of growth factors in the NP has proven to be quite challenging, as a straightforward injection only generates short-term effects [22, 70]. The optimal approach is to introduce the growth factors in a more permanent way by, for instance, gene transfer therapy [6]. Applying this approach implies the introduction of a gene responsible for growth factor production into the target cells which ideally results in a continuous production of the growth factor [2]. Alternatively, the introduction of new cellular material might be essential as IVD tissue is characterized by a very low cellular density and DDD decreases this density even further. As a result, a stimulation of the ECM production in the native cells will not yield sufficient ECM [3]. To address this cellular shortage, research is also performed to investigate the possibilities to introduce new cellular tissue into the IVD [73]. A dual approach combining growth factors with the introduction of new cellular tissue is anticipated to give the best result [27, 31].

In order to introduce cells, injectable biomaterials or cell-seeded scaffolds can be applied. The former are generally in situ cross-linkable hydrogels showing similar biomechanics compared to the native NP [29, 81, 83]. Alternatively, a cell-seeded scaffold can be useful for more extensive injuries [5]. A non-exhaustive overview of the materials and cell sources applied is shown in Table 3.2.

Injectable procedures show some benefits compared to methods, which require surgical implantation. First, injectable procedures are

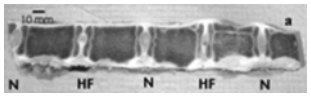
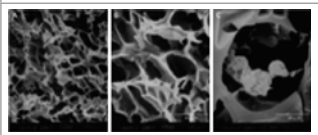
Table 3.2 Materials applied for tissue engineering of the nucleus pulposus (at present, all these "therapies" are considered to be experimental; therefore, no EBM indication is given)

Material class	Applied materials	Material properties	Cell source	Description	Benefits/drawbacks	Stage	Illustrations
Injectable							
Collagen	Collagen	*Protein *Main ECM constituent	*Rabbit NP cells *Human mesenchymal stem cells (MSCs)	Rabbit and human MSCs encapsulated in collagen microspheres containing rabbit NP-derived ECM, followed by injection into rabbit IVDs [75, 92]	+Higher hydration level observed +hMSCs survived and synthesized new ECM +Increase in type II collagen production and GAGs -Further optimization of culture conditions required	*In vitro, 24 days *In vivo, 6 months	 X-ray image of inserted NP materials in rabbits (Reprinted from [75] with permission from Elsevier)
	Collagen II/ PEG/HA	*ECM components *4S-starPEG is nontoxic cross-linker	*Rabbit adipose-derived stem cells	*Collagen II hydrogels in situ cross-linked 4S-starPEG cross-linkers [85]	+High NP cell viability +HA stimulates ECM synthesis, proliferation, migration and phenotype maintenance +HA is anti-inflammatory and anti-vascular +Ideal setting time (1 h) for clinical applications +Stable in culture -Poor mechanical properties of non-cross-linked collagen II	*In vitro, 14 days	 Picture of a seeded NP hydrogel (Reprinted from [85] with permission from Elsevier)
	Atelocollagen	*ECM component in NP	*Rabbit MSCs *Bovine NP	*Injectable + in situ cross-linkable *Enzymatic cross-linking using mTGase [11, 93]	+Ideal for injection +Good biocompatibility -Animal origin, risk for disease transfer -Weak mechanical properties -Degradative resistance properties -Scaffold size reduction observed after 7 days	*In vivo, 8 weeks	

Cellulose	Cellulose composite	*Polysaccharide fibers to tune mechanical properties	*Human, fetal cartilage cells	Injection in the NP in the absence of cells [81]	+Mechanical properties are maintained for a long period +In situ UV curing in novel surgical approach +Biocompatible	*In vitro, 1 week	 Cryo-SEM image of the composite hydrogel, showing a porous structure (Reprinted from [81] with permission from Elsevier)
Gelatin	Gelatin	*Derived from collagen (ECM component)	*Rabbit MSCs	Fibrinous gelatin + MSCs + growth factors injected in the NP [31]	+Decrease in disk height was slowed down +Increase in aggrecan and collagen type II +Decrease in collagen type I +Lower apoptosis rates +Injectable	*In vivo, 12 weeks	 Presence of a lot of spindle cells in the NP after 12 weeks (Reprinted from [31] with permission from Elsevier)
	Ferulic acid-gelatin/ chitosan/ glycerol phosphate	*Therapeutic effect, anti-inflammatory, antioxidant	*Rabbit NP cells	*Thermosensitive hydrogel as carrier for ferulic acid in NP repair, liquid at room temperature, turns into a gel at physiological temperatures *FA attached to gelatin through amide bond formation [94]	+No cytotoxicity +Good gelation and handling properties for clinical application +FA leads to a reduction in inflammation +Upregulation of collagen II and aggrecan +FA prevents proteoglycan degeneration	*In vitro, 3 days	
	oxi-HAG-ADH (hyaluronic acid-gelatin-adipic acid dihydrazide hydrogels)	*Components of ECM in NP	*Rabbit NP cells	Injectable hydrogel combined with NP cells and cross-linked using EDC and NHS [20]	+Sterilizable +Comparable viscoelastic properties -Cross-linking required -Slight drop in cell viability due to unreacted aldehyde groups	*In vitro, 1 week	 Confocal image of the cell morphology after 5 days in culture (Reprinted from [20] with permission from Elsevier)

(continued)

Table 3.2 (continued)

Material class	Applied materials	Material properties	Cell source	Description	Benefits/drawbacks	Stage	Illustrations
Hyaluronic acid	Hyaluronan HYAFF 120 and HYADD 3	*Major component of NP	*Pig bone marrow stem cells	*Injection of hyaluronan and homologous bone marrow stem cells [18]	+No fibrous tissue replacement or disruption of bony end plates +Large amount of chondrocytes in center of the disk +No necrosis or inflammation +Good cell viability +Straightforward +Cost-effective	*In vivo, 6 weeks	 Appearance of HYAFF® 120 (HF) injected and adjacent normal (N) disks 6 weeks after injection treatment of nucleotomized disks. Note biconvexity in the central part of the disk (Reprinted from [18] (Fig. 3.3) with kind permission from Springer Science and Business Media)
	Oxi-HA/ADH	*ECM component	*Six month old rabbit NP cells	*Injectable oxidized hyaluronic acid/adipic acid dihydrazide [23]	+Transforms from liquid to solid within minutes +Can maintain its shape for at least 5 weeks before degrading +Collagen type II and aggrecan formation +Nice mechanical properties +Good biocompatibility -Some cytotoxicity; not observed when increasing ADH percentage	*In vitro, 72 h	 SEM images of seeded hydrogels after lyophilization (Reprinted from [23] with permission from Elsevier)