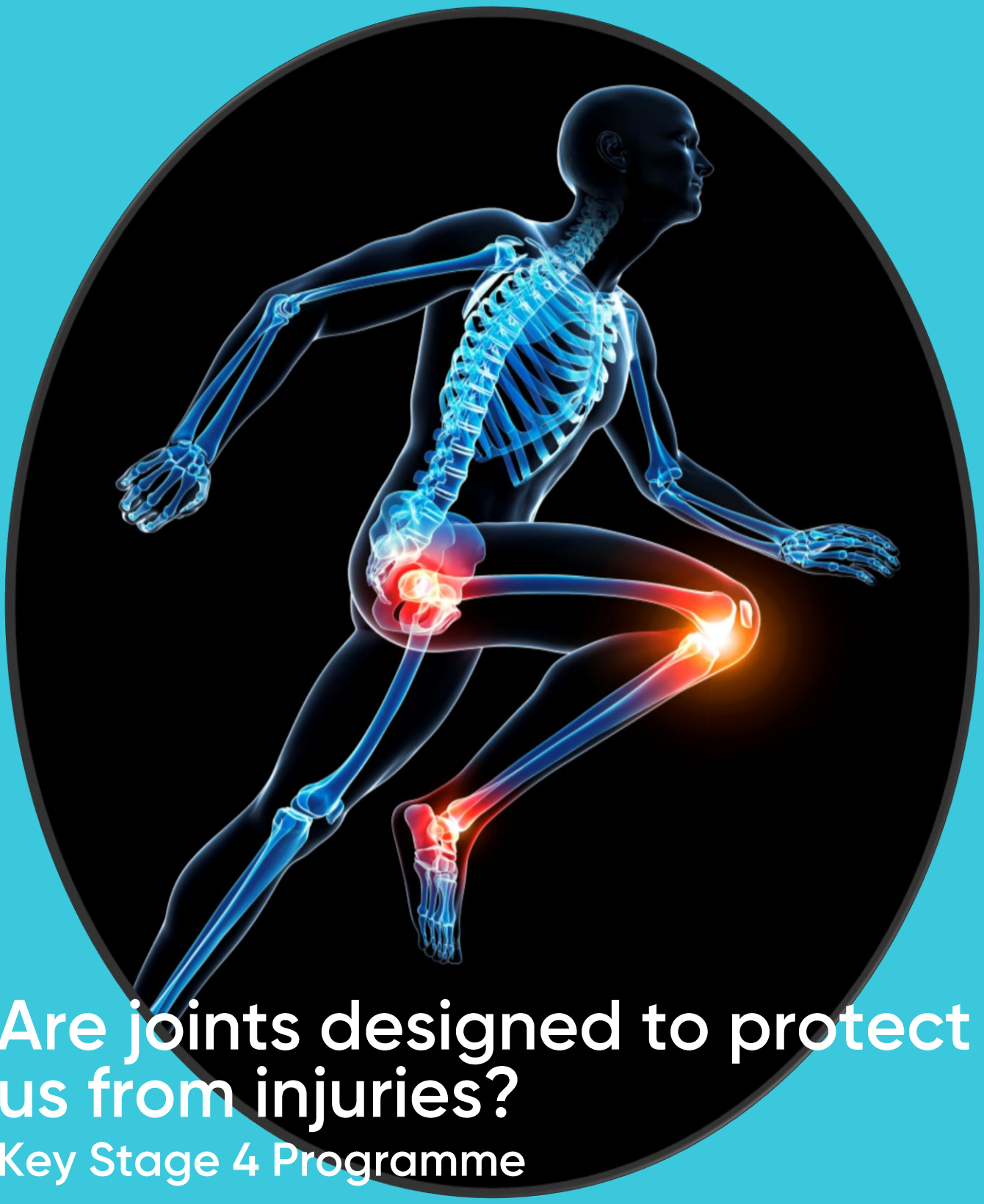

Are joints designed to protect us from injuries?

Key Stage 4 Programme

Pupil Name

Handbook Designed by Dr Kugan

Timetable and Assignment Submission

Timetable – Tutorials

1			
2			
3			
4			
5			
6 (Feedback)			

Timetable – Homework Assignments

Tutorial 1		
Tutorial 2		
Tutorial 3		
Tutorial 4		
Tutorial 5		

Assignment Submission – Lateness and Plagiarism

Lateness	
Submission after midnight on 9th August	10 marks deducted
Plagiarism	
Some plagiarism	10 marks deducted
Moderate plagiarism	20 marks deducted
Extreme plagiarism	Automatic fail

The Brilliant Club KS4 Programme – Pupil Feedback Report

Grade	Marks	What this means
1st	70+	Performing to an excellent standard at A level
2:1	60-69	Performing to a good standard at A level
2:2	50-59	Performing to an excellent standard at GCSE
3rd	40-49	Performing to a good standard at GCSE
Working towards a pass	0-39	Performing below a good standard at GCSE
Did not submit	DNS	No assignment received by The Brilliant Club

Lateness	
Any lateness	10 marks deducted
Plagiarism	
Some plagiarism	10 marks deducted
Moderate plagiarism	20 marks deducted
Extreme plagiarism	Automatic fail

Name of PhD Tutor			
Title of Assignment			
Name of Pupil			
Name of School			
ORIGINAL MARK / 100		FINAL MARK / 100	
DEDUCTED MARKS		FINAL GRADE	

If marks have been deducted (e.g. late submission, plagiarism) the PhD tutor should give an explanation in this section:

Learning Feedback Comment 1 - *Enter Key Learning Priority Here*	
What you did in relation to this Key Learning Priority *Enter feedback here*	How you could improve in the future *Enter feedback here*
Learning Feedback Comment 2 – *Enter Key Learning Priority Here*	
What you did in relation to this Key Learning Priority *Enter feedback here*	How you could improve in the future *Enter feedback here*
Learning Feedback Comment 3 – *Enter Key Learning Priority Here*	
What you did in relation to this Key Learning Priority *Enter feedback here*	How you could improve in the future *Enter feedback here*
Resilience Comment	

How you showed learning resilience during the course *Enter feedback here*	How you could build learning resilience in the future *Enter feedback here*

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Course Rationale

The aim of the course is to enhance the overall understanding of human joint function and fundamental properties of the joint will be addressed to understand possible reasons for joint failure. Human joints have specific properties that help to protect us from failure resulting in pain and discomfort. Unfortunately, the synovial joints in the human body are not designed to last us a lifetime and occasionally wear out. Over time, the cartilage layer, which covers the joint surfaces, tend to wear out and can result in osteoarthritis (cartilage breakdown).

In the UK alone 2.1 million have sought treatment for hip osteoarthritis, which was the second highest joint affected by osteoarthritis compared to ankle (1.8 million) and knee (5 million) (Arthritis Research UK, 2013). Therefore, end stage osteoarthritis will require surgical intervention. Sadly, although much research is still ongoing, many treatment options have not always been successful in various joints and there seems to be fundamental differences across the various joints in the human body. Although, the ankle joint is least affected by osteoarthritis, the implants last considerably lower number of years compared to knee and hip joints. Therefore, the ankle joint will be studied further and the reasons for why current treatment options for cartilage repair and joint replacements are unsuccessful will be addressed

Hence, the purpose of this course is to answer the question: 'Are joints designed to protect us from injuries?' by looking at joint anatomy, function, cartilage properties, changes in the joint after injury, process of cartilage breakdown, reasons for joint failure and possible treatment options.

Resources and Reading material

All provided in the course handbook

Final assignment (to be completed after Tutorial 5, page 35)

Part A (1000-word mini essay)

- You will write a mini essay on *''How are human joints designed to protect us from injuries''?*
- The essay should cover the following points
    - Introduce the topic, choose a joint and justify your choice *(max 200 words)*
    - Using images, describe the chosen joint in more detail in terms of structure and function *(max 200 words)*
    - Highlight the purpose of cartilage and the problems that could occur *(max 200 words)*
    - Discuss how human joint properties can help to protect the joint from failure *(max 200 words)*
    - Conclude by suggesting which joint is less susceptible to fail and why *(max 200 words)*

Part B (case study, max 1000-word essay)

An 18-year-old and 75-year-old have been suffering from a lot of pain in the ankle joint. They have recently been diagnosed with cartilage disease and concluded cartilage function to be poor. The doctors have made the decision to treat the ankle disease for both patients to restore ankle joint functions.

Address the following in your essay:

1. Write a brief intro to the task, relate to task 1 *(max 200 words)*
2. Detail the process of cartilage breakdown and suggest how each patient may have been affected by cartilage wear *(max 200 words)*
3. Summarise a few treatment options for treating osteoarthritis in the ankle joint *(max 200 words)*
4. Explain which method would be most suitable for each patient and why *(max 200 words)*
5. Suggest what other methods can be used to treat ankle disease and why *(max 200 words)*

Mark Scheme Table

	Skills	1st (70-100)	2:1 (60-69)	2:2 (50-59)
Subject knowledge	Knowledge and Understanding	○ All content included is relevant to the general topic and to the specific question/title ○ Good understanding of all the relevant topics. ○ Scientific terms are defined and used accurately throughout ○ Clear justification on how the content included is related to the specific issues that are the focus of the assignment	○ Most of the content included is relevant to the general topic and to the specific question/title ○ Good understanding of most the relevant topics ○ Scientific terms are used accurately but not always clearly defined. ○ Adequate justification on how the content included is related to the specific issues that are the focus of the assignment	○ Some of the content included is relevant to the general topic and to the specific question/title ○ Good understanding on some of the relevant topics but occasional confusion on others. ○ Scientific terms are used mostly accurately with occasional confusion and often not defined. ○ Some justification on how the content included is related to the specific issues that are the focus of the assignment

Critical thinking	Research and Evidence	○ Inclusion of rich sources of research findings, data, quotations or other sourced material as evidence for the claims/ ideas ○ Use evidence/calculations to support claims/assertions/ideas, consistently clearly and convincingly ○ Evidence of further reading beyond materials provided which were used in an appropriate context ○ Data is effectively analysed and appropriate assumptions/conclusions are reached	○ Inclusion of adequate sources of research findings, data, quotations or other sourced material as evidence for the claims/ ideas ○ Use evidence/calculations to support claims/assertions/ideas, mostly clearly and convincingly ○ Evidence of further reading beyond materials provided ○ Data is analysed and the assumptions/conclusions that are reached are mostly appropriate	○ Inclusion of some sources of research findings, data, quotations or other sourced material as evidence for the claims/ ideas ○ Use evidence/calculations to support claims/assertions/ideas, at times clearly and convincingly ○ Limited evidence of further reading beyond materials provided ○ There is an attempt to analyse data is and draw assumptions/conclusions
	Developing an Argument	○ A point of view or position in relation to the title or question is consistently clear ○ Argument/proof exceptionally well-developed and well-justified ○ A position is clearly established in relation to the question, and is developed effectively and consistently throughout the essay ○ Makes links effectively between subjects that have not previously been associated ○ Uses concepts from the tutorials in an unfamiliar context, and does so accurately and confidently.	○ A point of view or position in relation to the title or question is adequately clear ○ Argument/proof clear and well-developed and position justified ○ A position is established in relation to the question, and is well-developed in most of the essay ○ Some evidence of linking subjects that have not previously been associated ○ Use some concepts from the tutorials in an unfamiliar context, but not always accurate ○ Analysis of content to support the	○ A point of view or position in relation to the title or question is somewhat clear ○ Argument/proof clear but not well-developed ○ A position is established in relation to the question, and is well-developed in parts of the essay ○ Limited evidence of linking subjects that have not previously been associated ○ Limited use of concepts from the tutorials in other contexts ○ Some analysis of content to support the argument

		○ Content is analysed effectively to support the argument	argument	
	Critical Evaluation	○ Moved beyond description to an assessment of the value or significance of what is described ○ Evaluative points are consistently explicit/systematic/reasoned/justified ○ Effective critiques on the reliability of sources provided	○ Mostly description but some assessment of the value or significance of what is described ○ Evaluative points are mostly explicit/systematic/reasoned/justified ○ Some evidence of critiques on the reliability of sources provided	○ Only description with minimal assessment of the value or significance of what is described ○ Evaluative points are at times explicit/systematic/reasoned/justified ○ Limited evidence of critiques on the reliability of sources provided
Written communication	Structure and Presentation	○ Ideas are presented in paragraphs and arranged in a logical structure that is appropriate for the assignment ○ The introduction clearly outlines how the essay/report will deal with the issues ○ The conclusion summarises all the main points clearly and concisely ○ All calculations, formulas and methods are clearly structured, clear to follow and correct ○ Tables and graphs are effectively constructed including appropriate headings, units and scales. ○ All sources are referenced correctly in an agreed format	○ Ideas are presented in paragraphs and arranged in a structure that is mostly appropriate for the assignment ○ The introduction adequately describes how the essay/report will deal with the issues ○ The conclusion summarises most of the main points clearly ○ Calculations, formulas and methods are mostly structured, clear to follow and correct ○ Most tables and graphs are well constructed ○ Most sources are referenced correctly in an agreed format	○ Ideas are presented in paragraphs and arranged in a structure ○ The introduction mentions how the essay/report will deal with the issues ○ The conclusion summarises some of the main points clearly ○ Calculations, formulas and methods are not always structured, clear to follow and correct. ○ Some tables and graphs are well constructed but contains some errors ○ Some sources are referenced correctly in the agreed format with occasional errors

	Language and Style	○ No spelling, grammar or punctuation errors ○ Units and significant figures are presented accurately throughout ○ Writing style consistently clear, appropriate for scientific documents and easy to follow ○ Accurate and consistent use of technical language and vocabulary	○ Minimal spelling, grammar or punctuation errors ○ Units and significant figures are presented accurately throughout ○ Writing style mostly clear, appropriate for scientific documents and easy to follow ○ Some attempts of using technical language and vocab alary, but not always accurate	○ Some spelling, grammar or punctuation errors ○ Units and significant figures are presented accurately throughout with occasional errors ○ Writing style moderately clear, appropriate for scientific documents and easy to follow ○ Use of simple language and vocabulary effectively but struggles to use technical language

Glossary of Keywords

Word	Definition	In a sentence
MEDIAL		
LATERAL		
ANTERIOR		
POSTERIOR		
OAT Osteochondral autograft transplantation		
Total joint replacement (TJR)		
Fusion		
BMI		
Osteoarthritis		
Range of Motion		

Tutorial 1 – How does the human joint function?

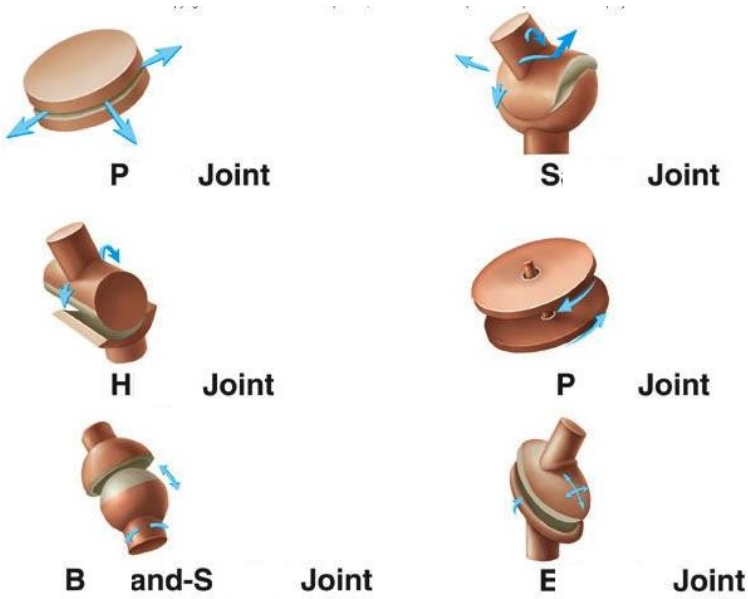
What is the Purpose of Tutorial 1?

- To name all joints in the body and the type of joints
- To identify a joint and to be able to label accurately
- To understand the purpose and function of cartilage

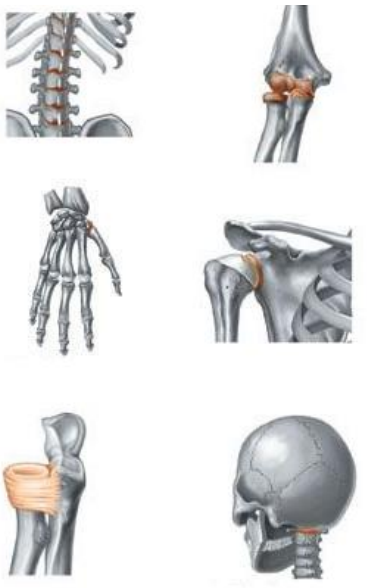
1.1 Name as many 'synovial joints' as you can in the human body.

1.2 Using the image below, in pairs complete the type of joints found in the human body. The first letters are given to help. Then match the type of synovial joints with an example given.

Type of Synovial Joints



Example of Synovial Joints



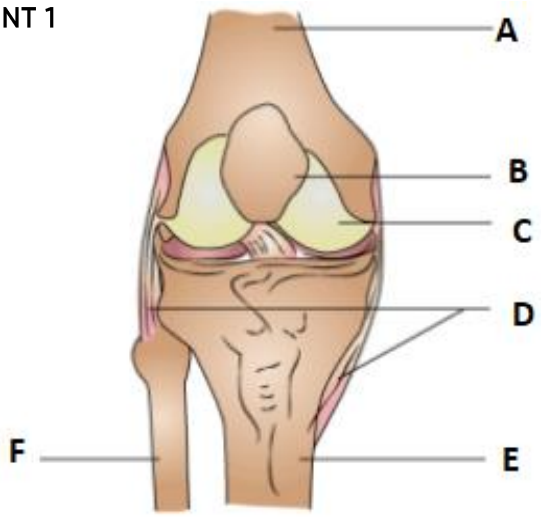
Notes

1.3 Next, name the joints below and label appropriately.

a) Firstly, name **JOINT 1** and **JOINT 2** as given below.

b) Complete the labelling of the joint given from A) to F).

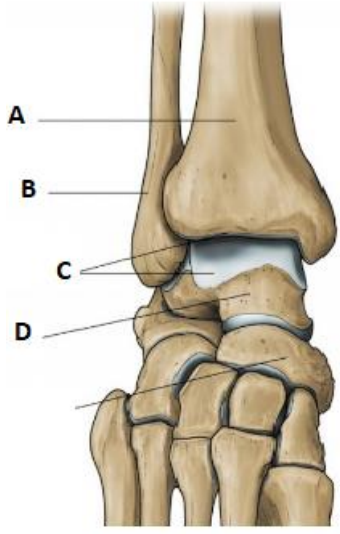
JOINT 1



1. Fibula (Lower Leg Bone)
2. Femur (Upper Leg/Thigh Bone)
3. Cartilage
4. Ligaments
5. Tibia (Shin Bone)
6. Patella (Knee Cap)

c) Complete the labelling of the joint given from A) to D).

JOINT 2



1.4 What do you think '*cartilage*' means? Write **one sentence** on a post-it note and **stick it** on the wall.

Homework 1: Baseline Test

The homework assignment for the first tutorial is a baseline test to see your initial level of attainment in this topic.
Do not worry how well/badly you perform on this baseline test. it takes into account that you may not be familiar with the subject area and only designed to help you and your teacher to identify where you are at the start of the programme to measure your progress along the way.

Part A) Think about anyone that commonly experiences joint pain. Share your story with everyone in the next tutorial.

Part B) In your own words, describe the following:

- Why pain occurs in the joint and is it common, if so why?
- Think about who is more likely to experience joint pain and why (i.e. age)
- What ways is joint pain treated? Name three.

1)

2)

3)

Tutorial 2 – How can cartilage properties be related to joint failure?

What is the Purpose of Tutorial 2?

- To list key properties of cartilage and the methods to define them
- To describe the process of joint failure from point of injury
- To describe concepts such as cartilage breakdown (osteoarthritis), cartilage lesions
- To be able to draw a healthy vs unhealthy joint and be able to understand the differences
- To demonstrate which joint is more likely to fail and why

2.1 In pairs, take **2 mins** to discuss and write down the meaning of *'cartilage property'*

2.2 Decide which ones are cartilage properties and which ones are not.

List	Property? Yes/No	What do you think this means?
Permeability		
Surface roughness		
Quantitative assay		
Thickness		
Indentation		
Young's modulus		
Histology		
Water content		
Cartilage breakdown		

(Note: Add in Glossary page)

2.3 Link the stages of cartilage breakdown in order (impact via injury to joint)

Stage 1

Stage 2

Stage 3

Stage 4

Stage 5

Fibrillation and erosion of cartilage surface

Injury to the joint

Changes in joint architecture occur and with further mechanical and inflammatory stress, disease progresses

Breakdown products induce an inflammatory response in the joint

Subsequent release of proteoglycans and collagen fragments into the joint environment

2.4 Name three reasons why cartilage breakdown may occur. Explain your reasoning.

1)

2)

3)

2.5 Draw a healthy vs unhealthy joint and state the differences. Use drawings on pg15 as guidance.

Healthy joint

Unhealthy joint

Tutorial 2 Homework:

As part of your homework assignment, prepare one 1-2 minutes presentation how cartilage breakdown affects the joints. You can make use of the whiteboard during your presentation, if you wish.

In your presentation address the following:

- What is cartilage?
- What are cartilage properties?
- Describe why cartilage breakdown occurs
- Briefly describe the breakdown process
- Conclude by addressing the differences between healthy and unhealthy joints.

For further reading:

https://www.medicalnewstoday.com/articles/171780.php

https://www.nhs.uk/conditions/cartilage-damage/Pages/Introduction.aspx

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3445147/

Tutorial 3 – What are the available treatment options?

What is the Purpose of Tutorial 3?

- To define non-surgical and surgical methods to treat joint related disorders
- To understand how age, weight, height, gender can impact on the function of the joint and influence on treatment methods

3.1 Which treatment method is either **surgical** or **non-surgical**? Tick the appropriate box.

Treatment methods	Surgical	Non-surgical
Metal resurfacing		
Cold Therapy		
Autologous chondrocyte implantation (ACI)		
Heat Therapy		
Osteochondral autologous transplantation (OAT)		
Arthroscopic Debridement		
Total joint replacement		
Physical Therapy		
Medications i.e. analgesics, pain killers		
Weight management		

3.2 In your own words, write down the descriptions for all treatment options. Compare your answers with your partner and be ready to share with the rest of the group.

Treatment methods	Description
Metal resurfacing	
Cold Therapy	
Autologous chondrocyte implantation (ACI)	
Heat Therapy	
Osteochondral autologous transplantation (OAT)	
Arthroscopic Debridement	
Total joint replacement	
Physical Therapy	
Medications i.e. analgesics, pain killers	
Weight management	

3.3 Body mass index calculations

BMI = Weight (kg) / height (meters squared) = kg/m^2

Using the above equation, calculate the body, mass index (BMI) for the following patients:

A. Female; age = 34; weight = 65 kg; height = 165 cm
B. Male; age = 52; weight = 81 kg; height = 176 cm
C. Female; age= 41; weight = 58 kg; height = 162 cm
D. Male; age = 18; weight = 60 kg; height = 171 cm
E. Male; age=31; weight= 91 kg; height= 172 cm
F. Female= 20; weight = 42 kg; height = 160 cm

BMI category

Adults	Women	Men
anorexia	< 17.5	
underweight	<19.1	<20.7
in normal range	19.1-25.8	20.7-26.4
marginally overweight	25.8-27.3	26.4-27.8
overweight	27.3-32.3	27.8-31.1
very overweight or obese	>32.3	>31.1
severely obese	35 – 40	
morbidly obese	40 – 50	
super obese	50 – 60	

Using these lined pages show your calculations and comment on which BMI category each patient falls under using the Table on **page 22.**

3.4 Repeat the following calculations using the following link

http://www.nhs.uk/Tools/Pages/Healthyweightcalculator.aspx (ask PhD tutor for help to access website)

3.5 Were there any *differences* between calculations in 3.2 and 3.3? Comment on the results.

3.6 Discuss the trend between age and gender for all six patients

a) For all six patients, complete the following table using the answers derived from 3.2. (Use your own derived BMI calculations).

Patient	Age	Gender	BMI
A			
B			
C			
D			
E			
F			

b) Draw an appropriate graph showing trend between gender, BMI and age for all six patients.

Tutorial 3 Homework:

As part of your homework assignment, can you look at the following scientific journal:

''Thickness of human articular cartilage in joints of the lower limb'' (Shepherd and Seedhom, 1999). Please refer Appendix on **page 41** *Or* Download this journal on the following link:
http://ard.bmj.com/content/annrheumdis/58/1/27.full.pdf

Task A

a) Summarise your understanding in your own words in a few sentences.
b) Was there any link to BMI, age and gender within this article? Highlight these.
c) From Table 1, calculate BMI from the given data and compare the results with the derived BMI. Were there any differences. Comment on the results.

Task B

In the next tutorial, be prepared to **share with everyone** what you found interesting and what you enjoyed the least and **why**.

Tutorial 4 – How does the ankle joint differ from other joints in the human body?

What is the Purpose of Tutorial 4?

- To describe the anatomy and function of ankle joint
- Be able to define range of motion (ROM) in a joint
- Be able to compare properties in two different joints by finding differences/similarities using i.e. ROM

4.1 Which bones form the ankle joint?

4.2 There are other names for the ankle joint. TRUE OR FALSE?

4.3 How many articulations are found in the ankle complex? Name all.

4.4 In your own words, describe the term *'Range of Motion (ROM)'*

4.5 On post-it notes, write down one activity that could be challenging for the ankle joint (Tip: consider the range of motion).

Refer to Tutorial 1 for the following questions:

4.6 What similarities/differences have you noticed between JOINT 1 and JOINT 2?

4.7 Discuss any differences/similarities in ROM between both joints? Identify other properties that could vary between these joints. Discuss in pairs and share with the rest of the group.

Tutorial 4 Homework:

As part of your homework assignment, read the following articles:

Article A
Cartilage degeneration in different human joints (Kuettner and Cole, 2005)

Please refer to Appendix **page 49** *Or* Download the journal on the following link:
http://www.oarsijournal.com/article/S1063-4584(04)00259-6/pdf

Article B
National Joint Registry Annual Report, 2015-2016

Download the report on the following link:

http://www.njrcentre.org.uk/njrcentre/Portals/0/Documents/England/Reports/13th%20Annual%20Report/07950%20NJR%20Annual%20Report%202016%20ONLINE%20REPORT.pdf

Task A
Using the Article A, compare ankle and knee cartilage properties.

In your answer, address the following:

- Introduce osteoarthritis disease
- Highlight the general features of knee and ankle cartilage (use Article A)
- Compare cartilage properties between both joints (i.e. biomechanical properties).

Task B
Using Article B (**sections 3.5 and 3.7**), compare outcomes of joint replacement surgeries of ankle and knee joints.

Tutorial 5 – Why are treatment options for the ankle joint unsuccessful compared to other joints?

What is the Purpose of Tutorial 5?

- To understand how ankle OA is diagnosed
- Be able to demonstrate name and detail three to four treatment options
- Be able to demonstrate treatment options in the ankle vs other joints

5.1 Which methods in the table below do you think are used to diagnose osteoarthritis in the ankle joint?

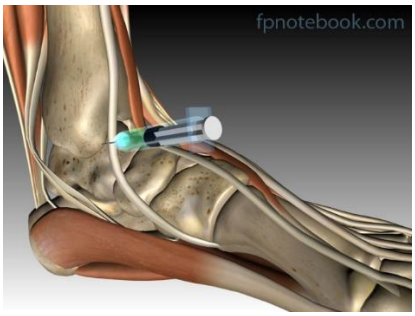
List	YES	NO
Medical history		
Custom shoes		
X-ray		
Canes/Braces		
Magnetic resonance imaging (MRI)		
CT scans		
Total joint replacement		

5.2 Remind yourself: What are the treatment options for osteoarthritis in the joint?

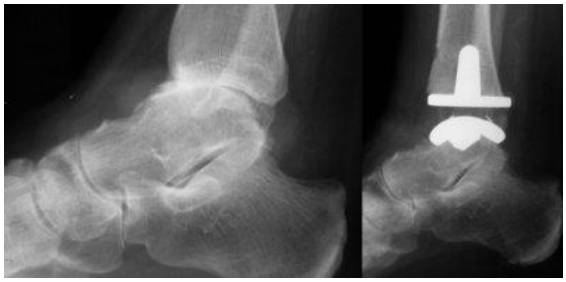
5.3 How else can ankle osteoarthritis be treated in addition to previously mentioned methods?

5.4 Name the following treatment methods:

A



B



C

D

E

F

Final assignment

Part A (1000-word mini essay)

- You will write a mini essay on *''How are human joints designed to protect us from injuries''?*
- The essay should cover the following points
    - Introduce the topic, choose a joint and justify your choice *(max 200 words)*
    - Using images, describe the chosen joint in more detail in terms of structure and function *(max 200 words)*
    - Highlight the purpose of cartilage and the problems that could occur *(max 200 words)*
    - Discuss how human joint properties can help to protect the joint from failure *(max 200 words)*
    - Conclude by suggesting which joint is less susceptible to fail and why *(max 200 words)*

Part B (case study, max 1000-word essay)

An 18-year-old and 75-year-old have been suffering from a lot of pain in the ankle joint. They have recently been diagnosed with cartilage disease and concluded cartilage function to be poor. The doctors have made the decision to treat the ankle disease for both patients to restore ankle joint functions.

Address the following in your essay:

6. Write a brief intro to the task, relate to task 1 *(max 200 words)*
7. Detail the process of cartilage breakdown and suggest how each patient may have been affected by cartilage wear *(max 200 words)*
8. Summarise a few treatment options for treating osteoarthritis in the ankle joint *(max 200 words)*
9. Explain which method would be most suitable for each patient and why *(max 200 words)*
10. Suggest what other methods can be used to treat ankle disease and why *(max 200 words)*

Tutorial 6 – Feedback tutorial

What is the Purpose of Tutorial 6?

- To receive feedback on final assignments.
- To share examples of best practice with the other pupils in your group.
- To write targets for improvement in school lessons.
- To reflect on the programme including what was enjoyed and what was challenging.

Final assignment feedback

What I did well...	What I could have improved on...
•	•
•	•
•	•

My target for future work is...

Reflecting on Uni Pathways

What did you most enjoy about Uni Pathways?
• • •

What did you find challenging about the programme?	How did you overcome these challenges?
• • •	• • •

Appendix 1 – Referencing correctly

When you get to university, you will need to include references in the assignments that you write, so we would like you to start getting into the habit of referencing in your Brilliant Club assignment. This is really important, because it will help you to avoid plagiarism. Plagiarism is when you take someone else's work or ideas and pass them off as your own. Whether plagiarism is deliberate or accidental, the consequences can be severe. In order to avoid losing marks in your final assignment, or even failing, you must be careful to reference your sources correctly.

What is a reference?

A reference is just a note in your assignment which says if you have referred to or been influenced by another source such as book, website or article. For example, if you use the internet to research a particular subject, and you want to include a specific piece of information from this website, you will need to reference it.

Why should I reference?

Referencing is important in your work for the following reasons:

- It gives credit to the authors of any sources you have referred to or been influenced by.
- It supports the arguments you make in your assignments.
- It demonstrates the variety of sources you have used.
- It helps to prevent you losing marks, or failing, due to plagiarism.

When should I use a reference?

You should use a reference when you:

- Quote directly from another source.
- Summarise or rephrase another piece of work.
- Include a specific statistic or fact from a source.

How do I reference?

There are a number of different ways of referencing, and these often vary depending on what subject you are studying. The most important to thing is to be consistent. This means that you need to stick to the same system throughout your whole assignment. Here is a basic system of referencing that you can use, which consists of the following two parts:

1. **A marker in your assignment**: After you have used a reference in your assignment (you have read something and included it in your work as a quote, or re-written it your own words) you should mark this is in your text with a number, e.g. [1]. The next time you use a reference you should use the next number, e.g. [2].
2. **Bibliography**: This is just a list of the references you have used in your assignment. In the bibliography, you list your references by the numbers you have used, and include as much information as you have about the reference. The list below gives what should be included for different sources.

    a. **Websites** – Author (if possible), title of the web page, website address, [date you accessed it, in square brackets].

    E.g. Dan Snow, 'How did so many soldiers survive the trenches?', http://www.bbc.co.uk/guides/z3kgjxs#zg2dtfr [11 July 2014].

    b. **Books** – Author, date published, title of book (in italics), pages where the information came from.

    E.g. S. Dubner and S. Levitt, (2006) *Freakonomics*, 7-9.

    c. **Articles** – Author, 'title of the article' (with quotation marks), *where the article comes from* (newspaper, journal etc.), date of the article.

    E.g. Maev Kennedy, 'The lights to go out across the UK to mark First World War's centenary', Guardian, 10 July 2014.

Appendix 2 – Using the VLE

VLE username	
VLE password	

Please remember the following key details...

- You are able log into the VLE either through the link on our website (**www.thebrilliantclub.org**) or going directly to the VLE site at (https://portal.thebrilliantclub.org/sign-in).
- Please update your profile with your full name and email address- this will allow you to retrieve forgotten passwords or usernames
- If you forget your log-in details you can request them to be emailed to you by clicking the link on the VLE home page. (If you are still having problems you can email: **schools@thebrilliantclub.org**)

What is the VLE?

The VLE is a virtual learning environment for all pupils on Uni Pathways it is used for:

- messaging your tutor
- submitting homework
- submitting your final assignment
- accessing resources for your tutorials
- finding out more information about university and careers

How should I use the VLE?

The VLE is a professional academic environment in which pupils are able to message their PhD Tutor. Here are a few things to consider:

- Ensure you keep a professional tone in the messages you send to your tutors.
- Ensure you always reply to your tutors in a timely manner.
- Thank your tutor for the effort they are putting in to give you your feedback etc.
- Submit all homework to your tutor on time.

IMPORTANT: Final assignment

- When you submit your final assignment, please remember that you need to do so through the **'My Activities'** tab and not as an attachment to a message.

Appendix 3 – Tutorial 3 Article

Ann Rheum Dis 1999;58:27–34

Thickness of human articular cartilage in joints of the lower limb

D E T Shepherd, B B Seedhom

Abstract

***Objectives*—(a) To determine the topographical variations in cartilage thickness over the entire surfaces of cadaveric lower limb joints, and (b) to examine the correlations between: cartilage thickness and its site specific modulus; cartilage thickness and donor age, weight, height, and body mass index.**

***Methods*—The cartilage thickness of 11 sets of cadaveric human joints each comprising an ankle, knee, and hip was measured using a needle probe technique. Statistical analysis was used to compare the cartilage thickness of the different lower limb joints and the differences in cartilage thickness over the surface of individual joints. It was further examined whether cartilage had a correlation with its stiffness, and any of the details of the specimen donors such as age, weight, height, and body mass index.**

***Results*—The mean cartilage thickness of the knee was significantly greater than that of the ankle and hip ($p<0.001$) in all 11 sets of joints, while the cartilage thickness of the hip was significantly greater than that of the ankle in 10 sets of joints ($p<0.001$). The mass of specimen donors was found to correlate with the mean cartilage thickness of all three lower limb joints. A correlation was also found between the height of donors and the mean cartilage thickness of the knee and hip joints, while only in the ankle joint was a correlation found between the mean cartilage thickness and the body mass index of the specimen donors. A further correlation was found between cartilage thickness and its modulus; the thinner the cartilage, the higher the modulus.**

***Conclusions*—The thickness of articular cartilage seems to be related to the congruance of a joint; thin cartilage is found in congruent joints such as the ankle, whereas thick cartilage is found in incongruent joints such as the knee. The correlations in this study imply that the larger and heavier was a donor the thicker was the cartilage in the lower limb joints. The data further suggest the presence of an inverse relation between the mean cartilage thickness and mean compressive modulus in each of the joints examined.**

(*Ann Rheum Dis* 1999;58:27–34)

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A vast array of techniques exist for measuring the thickness of articular cartilage. These methods include destructive techniques where the thickness of plugs or slices of cartilage are measured[1-4] or using a needle probe[5] and non-destructive techniques such as ultrasound.[6-8]

Jurvelin *et al*[9] did a comparison of optical, needle probe, and ultrasonic techniques for the measurement of articular cartilage thickness and concluded that each method had its limitations. One serious limitation was with ultrasound by having to assume a constant velocity of sound when it can vary greatly between cartilage specimens. Yao and Seedhom[10] have shown that the velocityof sound in cartilage can vary as much as 33.6% of the average calculated from a large number of sites, leading to errors in thickness of the same percentage when compared with data obtained by direct measurement using the needle probe technique.

More recent techniques used to measure the thickness of articular cartilage have included using magnetic resonance imaging.[11 12] Kladny *et al*[11] found that the mean percentage difference between cartilage thickness in magnetic resonance imaging and direct measurement from histological sections was about 10%, with the results most accurate for cartilage thicker than 2 mm.

Given the vast array of techniques that exist for measuring the thickness of articular cartilage it is surprising that few studies have been published giving detailed measurements of the thickness of human articular cartilage in joints of the lower limb. The thickness of articular cartilage influences both the stresses and strains arising within the cartilage matrix.[13] Detailed knowledge of cartilage thickness is also important for finite element work on synovial joints.

This paper presents the results of a study in which the cartilage thickness was surveyed over the entire surfaces of cadaveric lower limb joints. It further examines whether cartilage thickness had a correlation with its stiffness, and with any of the details of specimen donors such as age, weight, height, and body mass index.

Table 1 Details of specimen donors relevant to the study

Set number	*Sex*	*Age (y)*	*Mass (kg)*	*Height (m)*	*Body mass index (kg/m²)*
1	F	62	60	1.75	19.6
2	M	68	50	1.75	16.3
3	F	33	50	1.70	17.3
4	F	65	74	1.75	24.2
5	F	46	35	1.60	13.7
6	F	80	64	1.70	22.1
7	F	79	50	1.52	21.6
8	F	70	48	1.63	18.1
9	M	63	60	1.68	21.3
10	M	74	68	1.75	22.2
11	F	76	40	1.60	15.6
Mean		65.1	54.5	1.68	19.3
SD		14.3	11.9	0.08	3.3

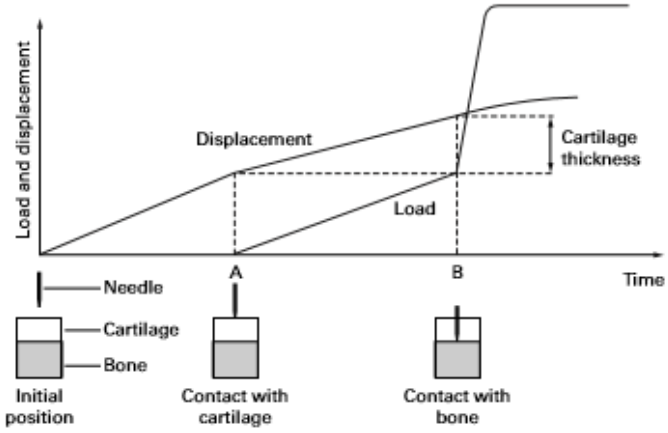

Figure 1 Response of load and displacement transducers for cartilage thickness measurement.

Methods

MATERIALS

Eleven sets of cadaveric human joints each comprising an ankle, knee, and hip were used in this study to measure the cartilage thickness over the whole surface of cadaveric lower limb joints. The joints within each set were obtained from the ipsilateral side and this meant that each joint in a set would have been subjected to the same number of loading cycles. Table 1 gives details of the specimen donors. Availability was a major limiting factor on the number of this type of specimens.

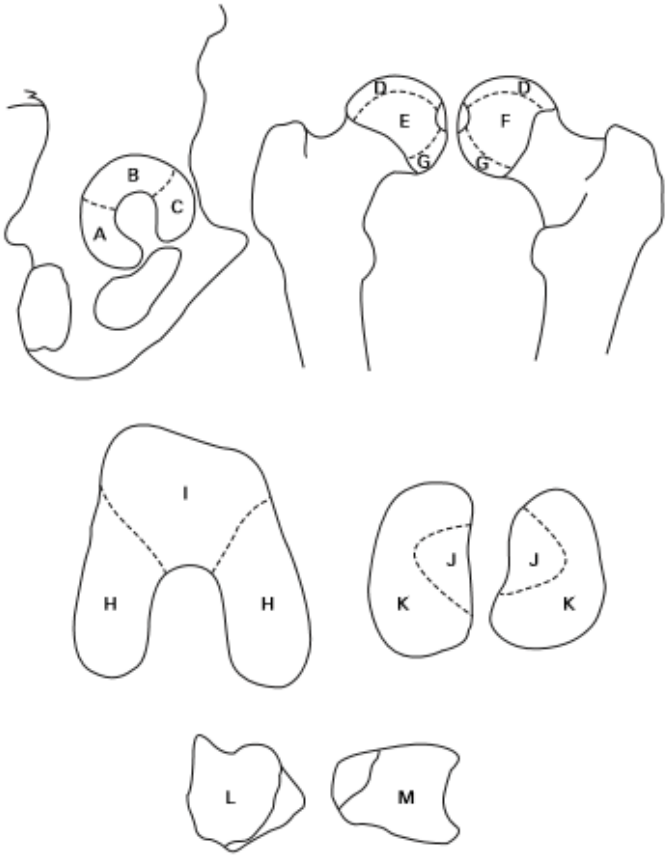

Figure 2 Distinct areas of the lower limb joints (A, B, C: posterior, superior, and anterior areas of the acetabulum respectively; D, E, F, G: superior, anterior, and posterior areas of the femoral head respectively; H, I: patellar surface and femoral condyles respectively; J, K: tibial areas of the knee covered by the menisci and those that come into direct contact with the femur respectively; L, M: talar and tibial areas of the ankle respectively).

SPECIMEN PREPARATION

Each set of joints was obtained from the mortuary within two to three days of death. The joints were sealed in plastic bags and stored at −20°C in a freezer until the time of testing, when the joints were thawed overnight in a refrigerator at 4°C. Once thawed, the surrounding tissue was removed from a joint so that the articular cartilage surfaces were exposed. A fine felt tip pen dipped in haematoxyline acid was used to draw a mesh over the entire articular surface of a joint yielding approximately 50 square test sites on the hip, 75 on the knee, and 35 on the ankle.

CARTILAGE THICKNESS MEASUREMENT

The cartilage thickness of each square (that did not show any visible signs of degeneration) on the mesh of all the articular surfaces was then measured using the technique of Swann and Seedhom.[5]

The method entails using an apparatus that allows a sharp needle to pierce the cartilage surface and move through the cartilage before coming to rest on the underlying bone at its interface with the cartilage. The apparatus also allowed simultaneous measurement to be taken of the displacement of the needle and of the load arising, from the moment the needle came into contact with the cartilage. From these measurements the cartilage thickness could be determined. The apparatus and technique have been previously described[5] and so, only a brief account of the procedure is given here.

The specimen is placed approximately 0.5 mm below the needle. The needle assembly shaft is released and moves towards the cartilage before piercing the surface. Figure 1 shows a typical response of the load and displacement signals with time as the needle is allowed to move through the cartilage and into the underlying bone. Before releasing the needle, both the load and displacement signals have zero values. Once the needle is released it moves towards the cartilage surface and the displacement signal thus begins to increase, but the load signal remains at zero because the needle is not yet in contact with the cartilage surface. At the moment the needle comes into contact with the cartilage surface the load signal increases above zero, thus identifying the exact position of the displacement signal that corresponds to the cartilage surface (point A in fig 1).

The contact point with the underlying bone can also be determined. As the underlying bone is much stiffer than articular cartilage, there is a very rapid positive increase in the load signal when the needle reaches the bone interface with cartilage (point B). The cartilage thickness is the difference in displacement between the contact point with the bone (point B) and the contact point with the cartilage surface (point A).

Table 2 Means and standard deviations of articular cartilage thickness of each ankle, knee, and hip within all 11 sets of joints and statistical comparisons. p Values from t test

	Mean (SD) mm			Statistical comparisons		
Set	Ankle	Knee	Hip	ank-kne	ank-hip	kne-hip
1	1.31(0.38)	2.51(0.49)	2.00(0.41)	p<0.001	p<0.001	p<0.001
2	1.14(0.17)	1.99(0.48)	1.65(0.41)	p<0.001	p<0.001	p<0.001
3	1.20(0.27)	1.97(0.42)	1.53(0.27)	p<0.001	p<0.001	p<0.001
4	1.62(0.25)	2.51(0.40)	1.71(0.60)	p<0.001	NS	p<0.001
5	1.25(0.22)	1.99(0.37)	1.54(0.27)	p<0.001	p<0.001	p<0.001
6	1.30(0.34)	2.23(0.50)	1.82(0.52)	p<0.001	p<0.001	p<0.001
7	1.19(0.34)	1.80(0.42)	1.40(0.23)	p<0.001	p<0.001	p<0.001
8	1.15(0.31)	2.55(0.45)	1.51(0.34)	p<0.001	p<0.001	p<0.001
9	1.30(0.29)	2.17(0.53)	1.67(0.33)	p<0.001	p<0.001	p<0.001
10	1.25(0.22)	2.42(0.48)	1.73(0.45)	p<0.001	p<0.001	p<0.001
11	1.00(0.20)	1.69(0.39)	1.35(0.30)	p<0.001	p<0.001	p<0.001

The load and displacement transducer signals were both sampled at 10 kHz thus enabling accurate measurements of the cartilage thickness to be made. The needle had a velocity of 60 mm/sec at the moment of contact with the cartilage surface and remains constant through the cartilage because there is very little resistance. As a sampling frequency of 10 kHz was used, this would lead to an error of 0.006 mm in the measurement of cartilage thickness and as this was typically in the range 1 to 3 mm, errors in the range 0.2 to 0.6% would be expected.

The repeatability of thickness measurements was previously investigated, using a similar apparatus, by Swann and Seedhom[5] who measured the thickness of a rubber strip glued on to a metal plate at 17 sites. A mean thickness of 1.4 mm was found with a standard deviation of 0.017 mm giving a low coefficient of variation of 1.2%. The mean value was also within 3% of the actual thickness of the rubber when measured directly with a micrometer.

STATISTICAL ANALYSIS OF THE CARTILAGE THICKNESS DATA

The means and standard deviations of the cartilage thickness were calculated for the whole surface of each ankle, knee, and hip within all 11 sets of joints. The cartilage thickness of each of these joints was found to be normally distributed as assessed using the Anderson-Darling normality test. The one sided independent two sample *t* test was therefore used to assess the significance of differences between the mean cartilage thickness of each ankle, knee, and hip within a set of joints.

The means and standard deviations of cartilage thickness were then determined for various distinct areas on each of the lower limb joints. The distinct areas on the hip were: the superior, anterior, posterior, and inferior areas of the femoral head, and the superior, anterior, and posterior areas of the acetabulum. The distinct areas of the knee were: the patellar and condylar surfaces of the femur, and on the tibia, those covered by the menisci and those areas that come into direct contact with the femur. The distinct areas of the ankle were those of the distal tibia and talus. Figure 2 shows these various distinct areas of the lower limb joints. The one sided independent two sample *t* test was used to assess the significance of differences between the mean cartilage thickness of the distinct areas on each lower limb joint.

Simple linear regression analyses were carried out to see if any correlation existed between the mean cartilage thickness of each lower limb joint and the details of the specimen donors (age, mass, height, and body mass index).

The same type of analyses were also performed to examine if any correlation existed between cartilage thickness of each lower limb joint and the compressive modulus of the articular cartilage. The compressive modulus data were determined by Shepherd[14] using an indentation technique described by Shepherd and Seedhom[15] in which the load is applied to the cartilage under physiological loading conditions.

The statistical significance level was set at the 5% level ($p<0.05$) for all statistical tests.

Results

MEAN THICKNESS OF THE ENTIRE SURFACES OF THE LOWER LIMB JOINTS

Within all 11 sets of joints the ankle always had the thinnest cartilage whereas the knee always had the thickest. Table 2 shows the means and standard deviations of cartilage thickness of each ankle, knee, and hip within all 11 sets of joints. The ankles and knees had mean cartilage thickness in the ranges 1.0 to 1.62 mm and 1.69 to 2.55 mm respectively, while the hips had mean cartilage thickness in the range 1.35 to 2.0 mm.

Table 2 also shows statistical comparisons of the mean cartilage thickness of each ankle, knee, and hip within a set of joints. The mean cartilage thickness of the knee was significantly greater than that of both the ankle and hip ($p<0.001$) within each sets of the 11 joints, while the cartilage thickness of the hip was significantly greater than that of the ankle within 10 of these sets ($p<0.001$).

TOPOGRAPHICAL VARIATION IN CARTILAGE THICKNESS

Hip

(a) Distinct areas of the femoral head

Four distinct areas on each femoral head, the superior, anterior, posterior, and inferior areas were compared. They had mean cartilage thickness in the ranges 1.41 to 2.25 mm, 1.46 to 2.09 mm, 1.26 to 1.98 mm, and 1.08 to 2.4 mm respectively. The means and standard

Table 3 Means and standard deviations of articular cartilage thickness of the distinct areas of each femoral head and acetabulum and statistical comparisons. p Values from t test

	Femoral head									
	Mean (SD) mm				*Statistical comparisons*					
Set	*Superior*	*Anterior*	*Posterior*	*Inferior*	*Sup-Ant*	*Sup-Pos*	*Sup-Inf*	*Ant-Pos*	*Ant-Inf*	*Pos-Inf*
1	1.61 (0.13)	2.09 (0.44)	—	2.40 (0.00)	p<0.05	—	—	—	—	—
2	1.78 (0.49)	1.67 (0.34)	1.70 (0.17)	1.08 (0.12)	NS	NS	p<0.05	NS	p<0.01	p<0.01
3	1.63 (0.38)	1.83 (0.00)	1.40 (0.18)	1.52 (0.08)	—	NS	NS	—	—	NS
4	2.25 (0.79)	1.75 (0.57)	1.98 (0.54)	1.51 (0.09)	NS	NS	p<0.05	NS	NS	p<0.05
5	1.78 (0.25)	1.58 (0.28)	1.56 (0.20)	1.50 (0.21)	NS	NS	p<0.05	NS	NS	NS
6	2.22 (0.50)	2.03 (0.42)	1.73 (0.45)	1.32 (0.24)	NS	p<0.05	p<0.001	NS	p<0.01	p<0.05
7	1.53 (0.15)	1.62 (0.27)	1.29 (0.12)	1.38 (0.25)	NS	p<0.001	NS	p<0.01	NS	NS
8	1.43 (0.42)	—	1.48 (0.15)	1.70 (0.01)	—	NS	NS	—	—	p<0.05
9	1.67 (0.27)	1.78 (0.29)	1.60 (0.32)	1.69 (0.48)	NS	NS	NS	NS	NS	NS
10	2.09 (0.49)	1.73 (0.41)	1.65 (0.37)	1.32 (0.03)	p<0.05	p<0.01	p<0.001	NS	p<0.001	p<0.01
11	1.41 (0.29)	1.46 (0.30)	1.26 (0.15)	1.31 (0.15)	NS	p<0.05	NS	p<0.01	p<0.05	NS

No comparison was possible because of severe degeneration of the cartilage where no statistical comparison is shown.

deviations of the cartilage thickness of these distinct areas are shown in table 3 together with the statistical comparisons of the mean cartilage thickness of the distinct areas on each femoral head.

Significant differences in mean cartilage thickness between the superior and anterior areas on the femoral head only occurred in sets 1 and 10. With set 1, the anterior area was significantly thicker than the posterior ($p<0.05$), while set number 10 showed the superior area to be significantly thicker than that of the anterior ($p<0.05$).

In four of the hip joints the superior area had cartilage that was significantly thicker than that of the posterior area ($p<0.001$ to $p<0.05$), while in five hip joints the superior area was significantly thicker than the inferior area ($p<0.001$ to $p<0.05$). The anterior area was found to have significantly thicker cartilage than the posterior area in two hip joints ($p<0.01$) and the inferior area in four hip joints ($p<0.001$ to $p<0.05$).

Comparison of the cartilage thickness of the posterior and inferior areas showed that the posterior area had significantly thicker cartilage in four hip joints ($p<0.01$ to $p<0.05$), while the inferior area had significantly thicker cartilage in one of the hip joints ($p<0.05$).

(b) Distinct areas of the acetabulum

Three distinct areas of each acetabulum were compared. These were the superior, anterior, and posterior areas and they had mean cartilage thickness in the ranges 1.24 to 2.25 mm, 1.2 to 1.71 mm, and 1.24 to 1.85 mm respectively. Table 3 shows the means and standard deviations of the cartilage thickness of these distinct areas.

Referring again to Table 3, it can be seen that only in two hip joints were any significant differences found in the mean cartilage thickness between the superior, anterior, and posterior areas of the acetabulum. In sets 2 and 9 the superior area had significantly thicker cartilage than the anterior area ($p<0.01$ to $p<0.05$). The posterior area was found to be significantly thicker than the anterior area ($p<0.01$) in set 2.

Knee

(a) Distinct areas of the femur

Two distinct areas of the femur were compared. These were the patellar surface and the femoral condyles and they had mean cartilage thickness in the ranges of 1.76 to 2.59 mm and 1.65 to 2.65 mm respectively. The means and standard deviations of the cartilage thickness of the distinct areas of each femur are shown in table 4 together with the statistical comparisons.

Five knee joints showed no significant difference in thickness between the patellar surface and the femoral condyles. In four knee joints the patellar surface had significantly thicker cartilage than the femoral condyles ($p<0.001$ to $p<0.05$) and in one knee joint (set 8) the femoral condyles had significantly thicker cartilage than the patellar surface ($p<0.001$). No comparison of cartilage thickness was possible for set number 6 because the patellar surface had full thickness cartilage loss and no areas could be tested.

Table 4 Means and standard deviations of articular cartilage thickness of the distinct areas of each femur and tibia and statistical comparisons. p Values from t test

	Femur			*Tibia*		
	Mean (SD) mm		*Stat*	*Mean (SD) mm*		*Stat*
Set	*Patellar surface*	*Condyles*	*Con-Pat*	*Covered*	*Direct*	*Cov-Dir*
1	2.59(0.34)	2.61(0.48)	NS	2.15(0.46)	2.87(0.49)	p<0.01
2	2.36(0.42)	2.05(0.47)	p<0.05	1.66(0.39)	2.13(0.26)	p<0.05
3	1.99(0.29)	1.83(0.30)	NS	1.97(0.35)	2.69(0.70)	p<0.05
4	2.49(0.32)	2.49(0.33)	NS	2.37(0.49)	2.83(0.46)	p<0.05
5	2.28(0.28)	2.00(0.38)	p<0.01	1.79(0.30)	2.07(0.37)	p<0.05
6	—	2.20(0.45)	—	2.27(0.61)	—	—
7	1.95(0.30)	1.65(0.29)	p<0.001	1.65(0.29)	2.63(0.60)	p<0.01
8	2.06(0.35)	2.65(0.34)	p<0.001	2.53(0.44)	2.98(0.26)	p<0.01
9	2.47(0.29)	1.99(0.45)	p<0.001	2.06(0.61)	2.56(0.61)	p<0.05
10	2.32(0.19)	2.53(0.45)	NS	2.09(0.37)	2.94(0.22)	p<0.001
11	1.76(0.34)	1.63(0.31)	NS	1.54(0.32)	2.20(0.51)	p<0.001

No comparison was possible because of severe degeneration of the cartilage where no statistical comparison is shown.

Acetabulum					
Mean (SD) mm			*Statistical comparisons*		
Superior	*Anterior*	*Posterior*	*Sup-Ant*	*Sup-Pos*	*Ant-Pos*
2.25 (0.24)	1.71 (0.45)	—	NS	—	—
1.95 (0.42)	1.34 (0.08)	1.85 (0.29)	p<0.01	NS	p<0.01
1.42 (0.02)	1.45 (0.20)	—	NS	—	—
1.35 (0.34)	1.33 (0.09)	1.31 (0.22)	NS	NS	NS
1.52 (0.28)	1.31 (0.16)	1.28 (0.28)	NS	NS	NS
1.51 (0.64)	1.62 (0.23)	1.55 (0.41)	NS	NS	NS
1.29 (0.21)	1.37 (0.29)	1.24 (0.17)	NS	NS	NS
1.49 (0.28)	1.46 (0.74)	1.71 (0.45)	NS	NS	NS
1.80 (0.39)	1.48 (0.21)	1.61 (0.16)	p<0.05	NS	NS
1.64 (0.37)	1.49 (0.37)	1.50 (0.20)	NS	NS	NS
1.24 (0.43)	1.20 (0.15)	1.36 (0.26)	NS	NS	NS

(b) Distinct areas of the tibia

Two distinct areas of the tibia were compared. These were the areas covered by the menisci and those that come into direct contact with the femur. The former had mean cartilage thickness in the ranges 1.54 to 2.53 mm and the latter 2.07 to 2.98 mm. The means and standard deviations of the cartilage thickness of these distinct areas of each tibia are shown in table 4 together with the statistical comparisons of the mean cartilage thickness of the same areas.

Within 10 knee joints, cartilage on those areas which come into direct contact with the femur was significantly thicker than cartilage on those areas covered by the menisci ($p<0.001$ to $p<0.05$). A comparison of the areas of the tibia covered by the menisci with those that come into direct contact with the femur was not possible for the knee in set number 6 because the cartilage on the latter areas was degenerate and no measurements were possible.

Ankle

In the 11 ankle joints the tibial and talar surfaces had mean cartilage thickness in the ranges of 1.06 to 1.63 mm and 0.94 to 1.62 mm respectively. Table 5 shows the means and standard deviations of the cartilage thickness of the tibial and talar surfaces within each ankle joint. The statistical comparisons of the mean cartilage within each ankle joint are also shown in table 5.

In seven ankle joints the tibia had significantly thicker cartilage than the talus ($p<0.001$ to $p<0.05$), while the remaining four ankle joints showed no significant difference in mean cartilage thickness between the tibial and the talar surfaces.

CORRELATIONS OF CARTILAGE THICKNESS WITH DETAILS OF SPECIMEN DONORS

Simple linear regression analyses were carried out to examine if any correlations existed between the mean cartilage thickness of various joints and the details of the specimen donors (age, mass, height, and body mass index).

No correlation was found between the age of donors and the mean cartilage thickness of any of the joints (fig 3A). However, significant correlations were found between the mass of donors and the mean cartilage thickness for each joint as can be seen in figure 3B. The coefficients of correlation and levels of signifi-

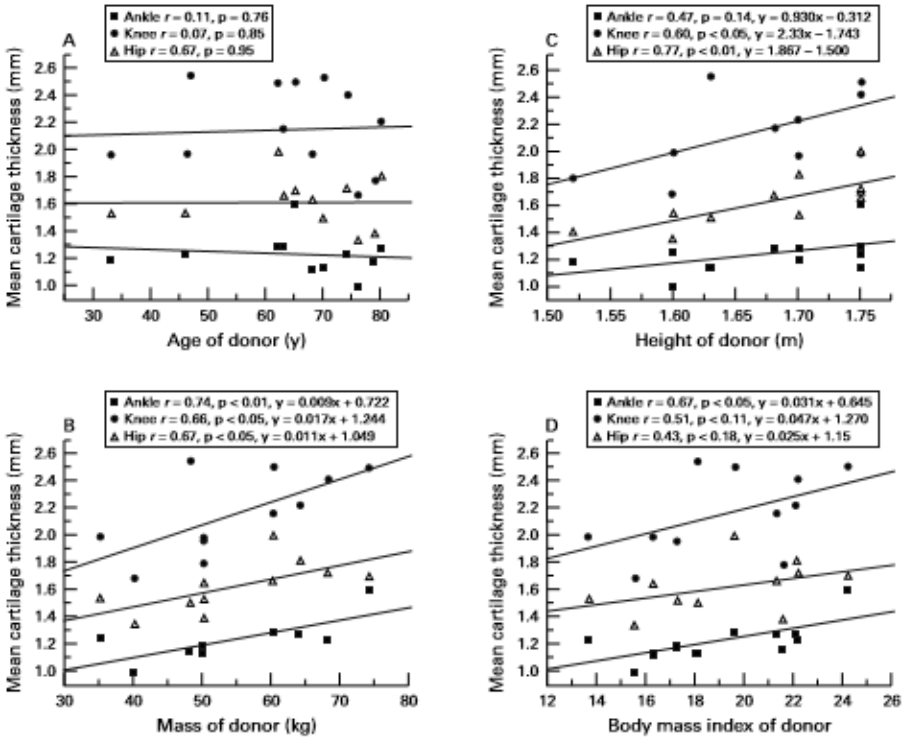

Figure 3 Variation of mean cartilage thickness of the lower limb joints with details of the specimen donors. (A) age, (B) mass, (C) height, (D) body mass index.

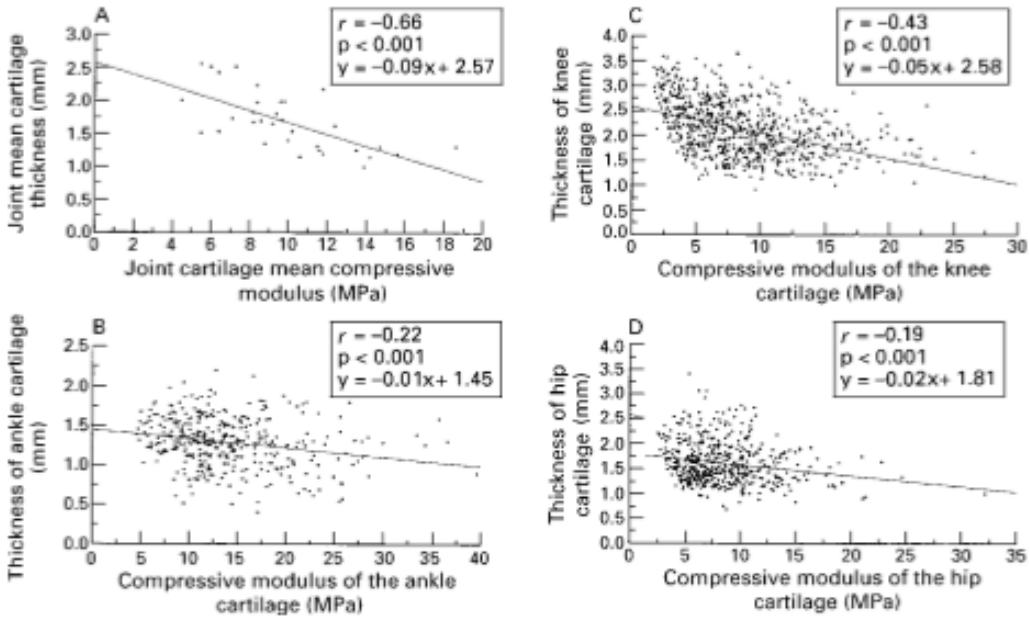

Figure 4 Variation of cartilage thickness modulus. (A) Each ankle, knee, and hip, (B) each site on all ankles, (C) each site on all knees, (D) each site on all hips.

cance between the mass of donors and the mean cartilage thickness of the ankle, knee, and hip joints were $r = 0.74$ at $p<0.01$, $r = 0.66$ at $p<0.05$, and $r = 0.67$ at $p<0.05$ respectively.

A significant correlation was also found between the height of donors and the mean cartilage thickness of the knee and hip joints as shown in figure 3C. The coefficients of correlation and levels of significance between the height of specimens and the mean cartilage thickness of the knee and hip joints were $r = 0.6$ at $p<0.05$ and $r = 0.77$ at $p<0.01$ respectively.

Furthermore, a significant correlation was found between the body mass index of the donors and the mean cartilage thickness of the ankle joint, as can be seen in figure 3D. The coefficient of correlation and level of significance between the body mass index of donors and the mean cartilage thickness of the ankle joint was $r = 0.67$ at $p<0.05$.

CARTILAGE THICKNESS AND CARTILAGE COMPRESSIVE MODULUS

The mean cartilage thickness of each ankle, knee, and hip was plotted against its mean articular cartilage compressive modulus (fig 4A). The data suggest an inverse relation between the thickness of articular cartilage and its compressive modulus. That is, thin cartilage has a high compressive modulus and thick cartilage a low compressive modulus.

A more detailed examination of the data was made using the cartilage thickness and compressive modulus data of each individual indentation test site from a joint surface, as shown in figures 4B, 4C, and 4D. Again the data confirm an inverse relation between the cartilage thickness and its compressive modulus. While the low p values indicate significance, the relatively low r values indicate a high scatter in the data.

Table 5 Means and standard deviations of articular cartilage thickness of the distinct areas of each ankle and statistical comparisons. p Values from t test

	Mean (SD) mm		*Stat*
Set	Tibia	Talus	Tib-Tal
1	1.57 (0.23)	1.16 (0.37)	p<0.01
2	1.18 (0.12)	1.11 (0.19)	NS
3	1.33 (0.14)	1.09 (0.30)	p<0.01
4	1.63 (0.15)	1.62 (0.29)	NS
5	1.23 (0.13)	1.28 (0.30)	NS
6	1.45 (0.17)	1.12 (0.39)	p<0.001
7	1.34 (0.11)	1.11 (0.39)	p<0.01
8	1.31 (0.24)	1.05 (0.31)	p<0.01
9	1.44 (0.18)	1.07 (0.27)	p<0.001
10	1.26 (0.13)	1.24 (0.26)	NS
11	1.06 (0.17)	0.94 (0.21)	p<0.05

Discussion

CARTILAGE THICKNESS AND JOINT CONGRUENCE WITH REFERENCE TO THE LOWER LIMB JOINTS

Examining the cartilage thickness data showed that the knee had significantly thicker cartilage than both the ankle and hip in all 11 sets of joints, while in 10 sets of joints the hip had significantly thicker cartilage than the ankle. Few explanations have been given in the medical literature as to the differences in cartilage thickness in joints, but Simon[3] proposed that the thickness of articular cartilage is related to the congruence of the joint; thin cartilage is found in congruent joints, whereas thick cartilage is found in incongruent joints.

In another study Simon *et al*[16] measured the congruence ratio (average length of the congruent surface divided by the average length of the total articular surface) and thickness of articular cartilage in the joints of dogs. They found that the knee had the thickest cartilage, the hip less thick, and the ankle thinner cartilage still as was also found in this study for human lower limb joints. An inverse relation was found between cartilage thickness and congruence ratio of the joint with thick cartilage correlating with low congruence of the joint and thin cartilage with high congruence.

Simon *et al*[16] suggested that the correlation between cartilage thickness and congruence

ratio of the joint tends to equalise the stress in congruent and incongruent joints. Congruent joints with thin cartilage only deform a small amount, yet the area of contact is large enough to distribute the load and maintain an acceptable level of stress. With incongruent joints deformation of the thick cartilage increases the contact area between the joint surfaces sufficiently to decrease the stress to an acceptable level.

CORRELATIONS OF CARTILAGE THICKNESS WITH DETAILS OF SPECIMEN DONORS

In this study the mean cartilage thickness of the lower limb joints were found to correlate with some of the details of the specimen donors. The mass of donors was found to correlate with the mean cartilage thickness of all three lower limb joints. Correlations were also found between the height of donors and the mean cartilage thickness of the knee and hip joints, while only in the ankle joint was a correlation found between the mean cartilage thickness and the body mass index of donors. These correlations imply that the larger and heavier a donor was the thicker the cartilage in the lower limb joints.

A possible explanation of this is given by Simon[13] who determined the thickness of articular cartilage in animals ranging in size from the mouse to the cow. He found that the thickness of articular cartilage generally increased with body size and there was a linear logarithmic relation between cartilage thickness and body weight. The same author concluded that the thickness of articular cartilage was scaled from small to large animals, according to the law of simple allometry. The law related growth of part of an organism to that of the whole. This could explain the positive correlations found in this study between the cartilage thickness of some of the lower limb joints and the mass, height and body mass index of the specimen donors. Hall and Wyshak[17] also found a correlation between the thickness of articular cartilage in the knee joint and the weight of patients, yet Armstrong and Gardner[18] could find no correlation between the thickness of femoral head cartilage and the body weight of specimen donors.

Although correlations were found between the cartilage thickness and some details of the specimen donors it should be highlighted that the samples in this study were mainly from elderly donors. The mean (SD) age of the donors was 65 (14) years and this should be kept in mind when considering the results. Indeed, this may explain why Armstrong and Gardner[18] found no correlation between the thickness of femoral head cartilage and the body weight of specimen donors because their specimens had an extended age range from 10 to 68 years.

CORRELATIONS OF CARTILAGE THICKNESS WITH ITS COMPRESSIVE MODULUS

In this study the data suggest an inverse relation between cartilage thickness and compressive modulus when the mean values of each ankle, knee, and hip are examined. When a more detailed examination was made of the site specific data of the cartilage thickness and compressive modulus, the low p values indicated significance yet the *r* values indicated a high scatter in the data.

Few studies have examined the correlation between the thickness of articular cartilage and its compressive modulus, but some published data suggest that no correlation exists. Simon[13] showed that cartilage thickness does not have a direct correlation with static compressive stress on the joint surface. Athanasiou *et al*[19 20] found no correlation between aggregate modulus of articular cartilage and its thickness. These two studies considered knee joint cartilage from five species (bovine, canine, human, monkey, and rabbit) and human hip cartilage respectively. Another more recent study[21] on the cartilage thickness in 15 pairs of ipsilateral human knees and ankles showed that cartilage thickness was significantly correlated with its stiffness expressed as the 2 s creep modulus. The present study, which is in agreement with this latter study, has also the advantage that sets of joints (ankle, knee, and hip) were obtained from the ipsilateral side and therefore the thickness of cartilage from knee joints from one population was not compared with hip or ankle joints from a different population.

The authors would like to thank Messrs M Pullan and B Whitham for their technical expertise and help with the experiments. This work was facilitated by a PhD scholarship from the University of Leeds.

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Historical images

Series editors: W Grassi, C Cervini

Figure 12 Hypertrophic osteopathy. Bernard L.
Dystrophies osseuses acquises d'origine obscure. In: Marfan A-B, Apert, Aviragnet, Bernard L, Garnier M, Hallé J, Milian. Maladies des os. Paris: Librairie J-B Baillière et fils, 1912.

Appendix 4 – Tutorial 4 Article A

OsteoArthritis and Cartilage (2005) 13, 93e103
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Osteoarthritis and Cartilage

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OARSI OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

Review

Cartilage degeneration in different human joints[1,2]

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Summary

Variations among joints in the initiation and progression of degeneration may be explained, in part, by metabolic, biochemical and biomechanical differences. Compared to the cartilage in the knee joint, ankle cartilage has a higher content of proteoglycans and water, as well as an increased rate of proteoglycan turnover and synthesis, all of which are responsible for its increased stiffness and reduced permeability. Chondrocytes within ankle cartilage have a decreased response to catabolic factors such as interleukin-1 and fibronectin fragments, compared to the chondrocytes of knee cartilage. Moreover, in response to damage, ankle chondrocytes synthesize proteoglycans at a higher rate than that found in knee cartilage chondrocytes, which suggests a greater capacity for repair. In addition to the cartilages of the two joints, the underlying bones also respond differently to degenerative changes. Taken together, these metabolic, biochemical and biomechanical differences may provide protection to the ankle.
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Key words: Knee, Ankle, Cartilage, Degeneration, Repair.

Introduction

Osteoarthritis (OA) is a degenerative joint disease that involves not only articular cartilage but also synovium, joint capsule and bone. OA is a common joint disease of the elderly; however, it does not affect all joints equally[1,2], even in those individuals with generalized OA. Certain features have been associated with the onset of generalized OA, but the question of why some joints are affected while others are not remains unanswered[2,3]. The joints that are most often affected by OA include the hip, knee, spine and metatarsophalangeal joints, as well as both the distal and proximal interphalangeal joints of the hand. The ankle, wrist, elbow and shoulder are generally spared from symptomatic OA. In these nonsymptomatic joints, degeneration of the articular cartilage does occur, suggesting that this degeneration may be nonprogressive, while in suscep-tible joints degeneration progresses to the disease state.

Poole et al.[4] have suggested that an imbalance between degeneration and repair might help to explain, in part, the differences among joints in susceptibility to OA. There have been almost no studies that have compared the cartilages from different adult human joints in an attempt to identify features within joints that might either retard or stimulate cartilage degeneration. We had originally proposed that susceptibility to OA is genetically programmed into the chondrocytes of some but not all joints. Our laboratories have concentrated on human articular cartilages of the ankle (talocrural joint) and the knee (tibiofemoral joint) from the ipsilateral limb (matched pairs) (Fig. 1) that are available to us through collaboration with the Gift of Hope Organ and Tissue Donor Network.

The knee and ankle were chosen for these studies not only for their availability through the tissue bank but also because of the dramatic differences in the prevalence of OA and degeneration between the two joints. While symptom-atic OA is extremely rare in the ankle joint (!0.1%), almost 10% of the population will develop this disease in the knee[5,6]. Although cartilage degeneration cannot be equated with OA, there is general agreement that degeneration precedes OA. There have been several studies[7,8], including our own[9e11], that have shown that full thickness defects of the cartilage are higher in the knee compared to the ankle.

It is well accepted that there are numerous anatomical and biomechanical differences between the knee and ankle joints that could account for more frequent degenerative changes in the knee than in the ankle. The knee joint is a relatively unstable joint composed of the distal femur, proximal tibia and patella; it is non-congruent and partially stabilized by menisci and ligaments as well as muscles. Movement in the knee joint is a mixture of flexion/extension and rotation. The talocrural (ankle) joint connects the foot and leg and, like the knee, is also made up of three bones: the distal tibia, distal fibula and the dome of the talus. Ligaments and the interosseous membrane between the tibia and fibula help to make this an extremely stable joint where movement is limited to extension/flexion. Under high loads the articular surfaces become highly congruent, transmitting the weight of the body from the tibia to all the other weight-bearing bones of the foot. The fact that the ankle surface is exposed to higher loads per unit surface

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[2]Based on the presentation by Dr Klaus E. Kuettner for the Osteoarthritis Research Society International (OARSI) Lifetime Achievement Award at The World Congress of the Osteoarthritis Research Society International in Berlin, Germany, October 2003.

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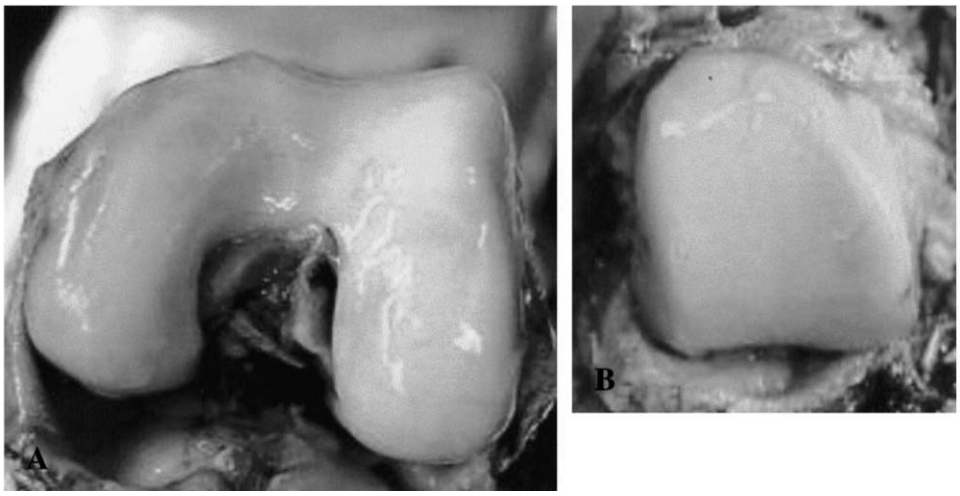

Fig. 1. Tibiofemoral and talocrural joints. (A) The distal femur and (B) the talus from a 36-year-old man. Both are Grade 0.

area than the knee in normal walking[12] would suggest that there are inherent properties of the ankle cartilage that protect it from the higher compressive loads it experiences.

In the lower limb, the risk factors for OA include abnormal biomechanics and trauma, obesity, age, genetic predisposition and higher bone mineral density, as well as congenital and developmental disorders of bones and joints[13]. OA of the knee is more common in women than in men and is associated with occupations in which there is high repetitive stress on the joint. OA also develops with altered joint mechanics that result following menisectomy or damage to the anterior cruciate ligament. In the ankle, the major risk factors are abnormal mechanics or trauma, and the only occupations associated with OA are ballet and soccer[14e17].

The anatomical and biomechanical differences between the two joints alone do not explain why the knee joint is more susceptible to OA than the ankle joint. We have proposed that there must be biochemical and molecular biologic differences between these two joints that provide some protection to the ankle. Our studies were designed to determine whether ankle cartilage is more resistant than knee cartilage to progressive degeneration and OA due to either one or all of the following criteria: 1) differences in biochemical composition and/or biomechanical properties of the extracellular matrix; 2) decreased response to catabolic factors; and 3) increased synthetic ability to repair. At the present time we have data to support all three components of this hypothesis.

Donor population

In order to compare human adult cartilages from knee and ankle, we established collaboration with the Gift of Hope Organ and Tissue Donor Network that has continued for more than 15 years. During that period we have been able to acquire knees and ankles from the ipsilateral limb of donors ranging in age from fetal to 90C years of age (Table I). In addition, we have acquired unmatched ankles for use in many of our cartilage studies including those on changes in cartilage with aging[18]. Our studies with the ankle cartilage have allowed us to establish the experimental parameters that we use for studying normal knee and ankle pairs that are available in more limited numbers.

The profiles of the donors from whom we receive joint tissue reflect the donor population available to the tissue bank[11]. That population consisted of 73% men and 27% women, of whom 91% were Caucasian, 6% African American, 2% Hispanic, and 1% Asian. The average age was 55.7 years. The most frequent causes of death were myocardial infarction or cardiopulmonary accident (72%), accidental death (16%) and stroke (12%). Of the adult donors that were assessed for weight, 33% of the women and 23% of the men were considered grossly overweight. Donor cartilages were excluded from our studies if the donor was being treated for joint disease (based on reports by the families of the donors) or had skeletal pathology, fractures, HIV, hepatitis or diabetes.

Joint grading scale

A five-point scale originally described by Collins[19] for OA of the knee was modified by Muehleman et al.[9] for use with the ankle (Fig. 2). In brief, the grades are as follows: Grade 0 joints display no signs of morphologic degenerative changes with a surface that is smoothly reflective and unfibrillated; Grade 1 joints have minimal fibrillations, shallow pits or grooves affecting the cartilage surface in the absence of degenerative changes in articular surface geometry; Grade 2 joints have deep fibrillations and fissuring, flaking, pitting and/or blistering, early marginal hyperplasia and, possibly, small osteophytes; Grade 3 joints have extensive fibrillations, fissuring, obvious osteo-phytes and 30% or less of the articular cartilage surface eroded down to the subchondral bone; and Grade 4 joints have prominent osteophytes and greater than 30% of the articular surface eroded down to the subchondral bone with gross geometric changes. Because osteophytes are ex-tremely rare on the talus, the overall grading system for this

Table I
Total number of donors and joints from whom articular cartilage was available through the Gift of Hope Organ and Tissue Donor Network between 1993e2003

Donors (Total)	2953	Joints (Total)	5746
Knee/ankle pairs	271	Knee/ankle pairs	507
Ankles only	2682	Ankles only	5239

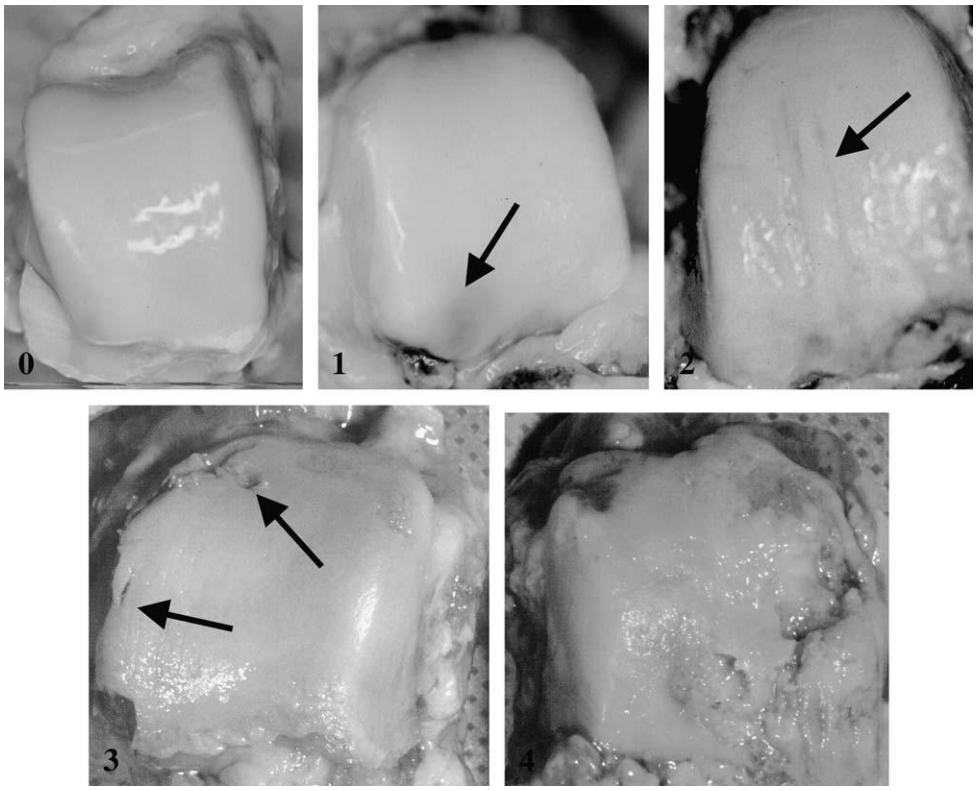

Fig. 2. The five-point grading scale applied to the talus. The grades are indicated as 0e4. Arrows point to areas of roughening (Grade 1), fissuring (Grade 2) or full thickness defect (Grade 3). On the Grade 4 talus, the dome is collapsed and more than 30% of the articular cartilage has been eroded to the subchondral bone. Reproduced from Cole et al.[11] with permission.

joint focused primarily on the disruption of the cartilage surface. The distribution of joint grades is listed in Table II. For our metabolic studies, we included both Grades 0 and 1 as normal because Grade 1 may simply represent normal senescent changes in the superficial cartilage that may not be progressive. Joints with Grades 2e4 were classified as degenerative.

Based on the data collected since 1993, we have been able to gain new insights into the degenerative changes in a population that has not been diagnosed with OA. While an increase in degenerative changes in the knee with age has long been accepted[20], it was not previously known whether the same was true for the ankle. Approximately 50% of the tali had articular surfaces with no macroscopically visible surface disruptions (Grade 0) compared with 30% of the femurs. When the ankle grades are analyzed by decade, it is clear that the percentage of those with Grade 0 decreased with increasing age; however, compared with the knee, progression is slower (Fig. 3)[11]. Interestingly, the percentage of Grade 0 ankles in the donors 90 years or older increased to over 50% while only 29% in the 80 year olds received Grade 0. In fact, none of the tali from donors in the ninth or tenth decades were Grade 3 or 4. This increase in Grade 0 tali may be due to the fact that cartilage degeneration in the ankles of those donors who live longer lives (O90 years of age) may be progressing even more slowly.

Table II
Distribution of joint grades. Percentage is based on 4005 ankles
and 405 knees that have been graded

Joint/Grade	0	1	2	3	4
Knee (%)	34	20	25	14	7
Ankle (%)	52	25	19	4.7	0.3

In the ankle, more men (53%) received Grades 2e4 than women (34%); in the knee, the percentage of higher grades was also greater in men but the difference was smaller (60% for women, 67% for men). When the gender differ-ences were analyzed based on weight, overweight men had higher grades than normal weight men for both the knee and ankle. Nearly 50% of the Grade 4 tali were obtained from overweight men.

In addition to the gender differences, there were other unexpected findings[10]. Our data show that the degree of degeneration in ankle cartilage is similar in both limbs in the majority of cases (79% had symmetrical scores). Addition-ally, in those donors with ankle cartilage degeneration, the ipsilateral knee cartilage also showed degenerative changes of an equal or higher grade. These two un-expected findings suggest that factors, such as altered biomechanics, responsible for degeneration in one limb also cause changes in the contralateral limb and influence both the ankle and knee ipsilateral joints.

Adult articular cartilage from the knee and ankle

Both knee and ankle cartilages have general features that are typical of articular cartilage[21] in that there are no blood vessels or nerve supply, and nutrition is derived from the synovial fluid. Articular cartilage protects the underlying more rigid bone by providing elasticity and resistance to compressive forces. These properties are conferred by the two major matrix constituents of the cartilage extracellular

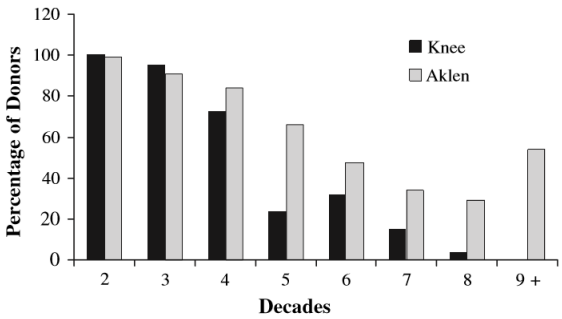

Fig. 3. Percentage of Grade 0 by decade in knee and ankle. The distribution of grades is based on data from 4005 tali and 409 femurs. Donors included in the ninthC decade were 81 to 96 years of age. Adapted from Cole et al.[11] with permission from the Orthopaedic Research Society.

matrix: collagens and proteoglycans. The abundant extra-cellular organic matrix (98% by volume) of cartilage is synthesized and maintained by a few sparsely distributed cells, the chondrocytes.

In both joints, the articular cartilage can be divided into three main layers e the superficial, middle and deep (Fig. 4). The matrix of the superficial layer, which contains flat, disc-shaped chondrocytes, has a relatively low proteoglycan content and collagen fibers parallel to the surface. In both joints, these specialized superficial layer cells, but not the chondrocytes deeper in the cartilage, secrete the superficial zone protein, or SZP, into the synovial fluid[22,23]. In the middle and deep zones, the chondrocytes are more spherical; the matrix has a higher content of proteoglycan and the collagen orientation changes from isotropic in the middle to perpendicular to the surface in the deep layers. The articular cartilage in the ankle is fairly uniform in thickness (1e1.5 mm) across the entire surface, while the cartilage of the knee varies from 2e6 mm in thickness. The major difference between the two cartilages appears to be the thickness of the middle and deep layers[24,25]. In the superficial layer, the chondrocytes are organized into chondrons[26]; the chondrons in the knee are composed primarily of single cells, while the chondrons in the ankle are organized into clusters of two to four cells each. While there is a dramatic decline in cellular density between young infants and adult cartilage in both the superficial and deep layers[27], in the adult the cell density does not change with age in normal cartilage. The cell densities of the superficial layers of the knee and ankle are similar, as are the cell densities of the deep layers[28].

To analyze changes in cartilage with age in our initial studies[18], we used ankle cartilage because 50% of the donor talar cartilages were normal (Grade 0). These analyses show that neither the content of type II collagen (128 G 14 mg/ml wet weight) nor sulfated glycosaminoglycans (40.6 G 14 mg/mg wet weight) changed with increasing age between 13 and 75 years. However, there is continuing synthesis and degradation of the matrix components throughout life that is primarily associated with the cell and its pericellular matrix. Type II collagen synthesis was identified by mRNA and the C-propeptide (CPII) by immunoassay. The initial proteolytic processing of the collagen by collagenases and its subsequent denaturation were also measured by immunoassay for the collagenase cleavage and the denaturation neoepitope. While the cleaved type II collagen showed a trend toward increasing with age, the ratio of cleaved to denatured type II collagen did show a significant increase. These data suggest that in normal articular cartilage a homeostasis exists with regard to the turnover of matrix components and that this predominantly pericellular turnover continues throughout life. These studies would further suggest that the talar cartilage may provide an excellent model for studying changes in cartilage with aging that are distinct from changes with degeneration as are often found in the knee.

Comparison of knee and ankle cartilage

BIOCHEMICAL COMPOSITION AND BIOMECHANICAL PROPERTIES

Our data have shown that there are significant differences in the biochemical composition and biomechanical properties of the ankle cartilage matrix compared to that of the knee (Fig. 5)[29]. For example, in the ankle, the sulfated glycosaminoglycan content is significantly higher and the water content is significantly lower; however, there is no difference in collagen content. The dynamic stiffness is higher in ankle cartilage than in knee cartilage, while the

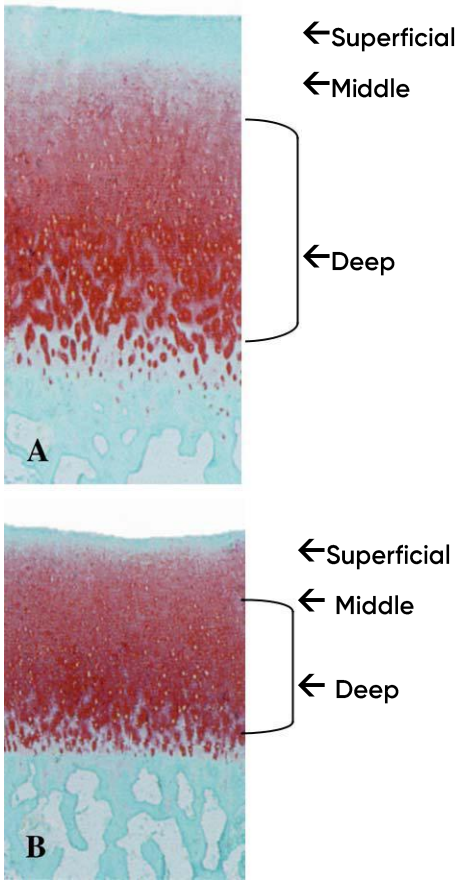

Fig. 4. Histological sections of full thickness articular cartilage and subchondral bone from the femur (A) and talus (B) of a 52-year-old man that were stained with Safranin O and fast green. The relative positions of the superficial, middle and deep layers of the cartilage are shown. (Original magnification Z 4!.)

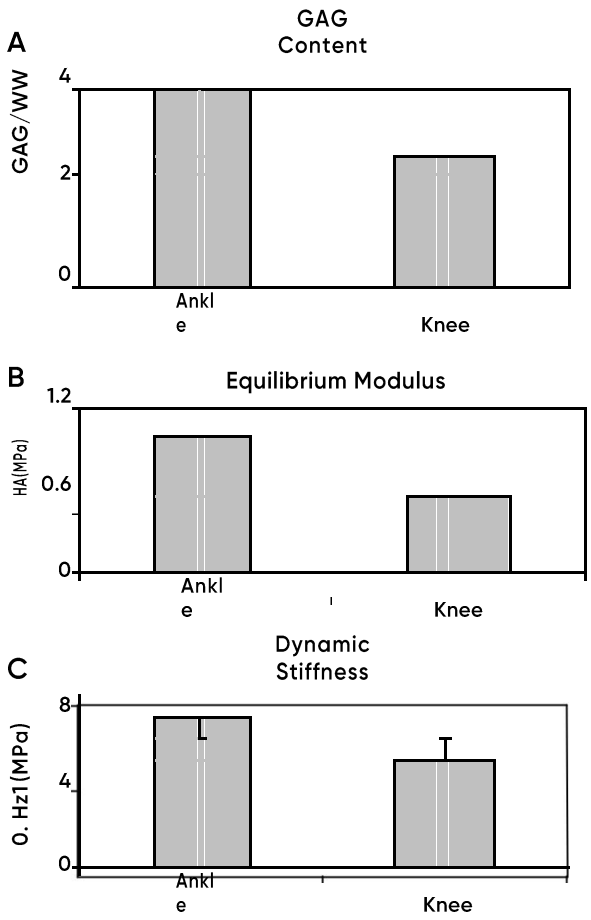

Fig. 5. A comparison of glycosaminoglycan (GAG) content (A), equilibrium modulus (B), and dynamic stiffness (C) of the femur of the knee and the talus from the ankle. Bars correspond to the mean C S.E.; differences were assessed by analysis of variance and Fisher's least significant difference test, *indicated P ! 0.01. Adapted from Treppo et al.[29] with permission from the Orthopaedic Research Society.

hydraulic permeability is lower, reflecting the decreased water content and higher sulfated glycosaminoglycan content of the ankle cartilage. These properties could benefit the ankle cartilage by increasing cartilage stiffness, thereby protecting the cartilage from the deleterious effects of higher compressive forces.

The higher compressive stiffness of the ankle cartilage compared to that of the knee was apparent when the two cartilages were subjected to injurious compression[30]. In order to produce levels of peak stress and visible damage to human cartilage, a 65% final strain was required producing peak stresses of 11 G 1 MPa in knee cartilage and 16 G 1 MPa in ankle cartilage. This compression resulted in macroscopic tissue changes to 81% of the knees but only 17% of the ankles.

DIFFERENCES IN SYNTHESIS OF PROTEOGLYCANS

The higher sulfated glycosaminoglycan content of ankle cartilage correlates with a higher rate of synthesis by ankle chondrocytes[31]. When cartilages from the two joints were assayed in explant culture for differences in synthesis, ankle cartilage had a higher incorporation rate (mean Z28,799 cpm/mg DNA) than those from the knee

(mean Z15,510 cpm/mg DNA) (Fig. 6). These differences were maintained over 25 days in culture[27] and begin early in development because they were found in donors as young as 1-year old[31]. In addition, ankle cartilage has also been shown to have higher levels of protein synthesis than knee cartilage[32].

When the turnover of proteoglycans in knee and ankle cartilages was compared[33], the half-life in knee cartilage was 22.68 days while that in ankle cartilage was 16.58 days. This reduction in the half-life implies that the ankle is metabolically more active not only in synthesizing proteo-glycans but also in their degradation. While we do not know at the present time which proteoglycans are responsible, our data have shown that there are 2.1 times higher levels of aggrecan mRNA in ankle chondrocytes compared to those in the knee. Because aggrecan contains the majority of the sulfated glycosaminoglycans in the cartilage, it is probable that this proteoglycan is principally responsible for the differences.

MODULATION OF SYNTHESIS BY MECHANICAL COMPRESSION

The synthesis of proteoglycans, collagens and other proteins can be modulated by static as well as dynamic mechanical compression; static compression (O10%) has been previously shown to inhibit proteoglycan and protein synthesis in a dose-dependent manner in bovine calf cartilage[34,35]. When knee and ankle cartilages were subjected to increasing static compression (0e50%), pro-teoglycan, collagen and protein synthesis in both the knee and ankle were altered[32,36]. In the ankle, collagen synthesis was suppressed by 15% compression while the synthesis of proteoglycans and protein were not significantly sup-pressed until the higher strain of 25e50% compression was applied. Without compression, ankle chondrocytes synthe-sized significantly more protein than those of the knee; with compression, protein synthesis was increased in knee chondrocytes to levels similar to those of the ankle chondrocytes. In the ankle, dynamic compression caused

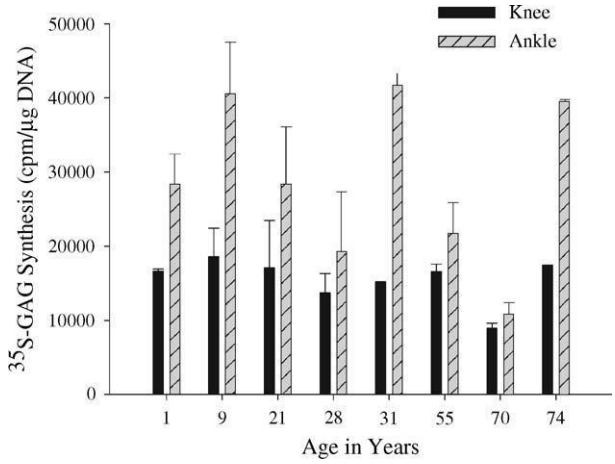

Fig. 6. Synthesis of glycosaminoglycans (GAG) by matched pairs of knee and ankle chondrocytes. ^{35}S-incorporation into GAG as cpm per mg DNA was measured in explants for 4 h after 3 days in culture. Each measurement is the mean G S.D. in the knee (closed columns) and ankle (hatched columns) of triplicate samples from matched pairs (P Z 0.047). Reprinted from Eger et al.[31] with permission from the Orthopaedic Research Society.

a significant increase in the synthesis of collagen and total protein, but not of proteoglycans. Dynamic loading caused an increase in protein synthesis across all ages tested, emphasizing the importance of regular loading to maintain cartilage integrity. If knee and ankle chondrocytes were first stripped of their matrices, then seeded into agarose and allowed to resynthesize a matrix before compression, the response to loading by both knee and ankle chondrocytes was no longer significantly different. These data suggested that the differences between knee and ankle chondrocytes are not genetically programmed into the cells and in addition, this supports a role of the extracellular matrix in regulating cellular activity. Because adult articular cartilage provides a stable microenvironment for the chondrocytes with extremely low rates of turnover[37,38], the presence of the native matrix is thought to be important in regulating chondrocyte metabolism.

MAINTENANCE OF CHONDROCYTE PHENOTYPE

Further data from knee and ankle chondrocytes provide additional supporting evidence that the extracellular matrix plays a role in influencing synthesis. If that matrix is first removed and the denuded chondrocytes are allowed to synthesize a new matrix in alginate beads, there were no longer significant differences in glycosaminoglycan synthe-sis[39], nor were there significant differences in their half-lives. However, differences in the response of knee and ankle chondrocytes to the catabolic cytokine, interleukin-1b (IL-1b), were maintained.

DIFFERENCES IN RESPONSE TO CATABOLIC FACTORS

Interleukin-1 (IL-1) at low concentrations is a proinflammatory catabolic cytokine that has two distinct effects on human chondrocytes (Fig. 7): at lower concentrations it suppresses the production of matrix components and in higher concentrations stimulates the synthesis of proteolytic enzymes and the degradation of extracellular matrix components, thereby shifting the metabolic balance from anabolism to catabolism[40]. OA may be regarded as a disorder of cartilage matrix metabolism with intermittent inflammatory episodes superimposed. During these inflammatory events, IL-1 is released from the inflamed synovial tissue where it is capable of entering the cartilage. The concentration of IL-1 measured in the synovial fluid from the joints of patients with arthritis ranges from 13e402 pg/ml[41]. The response of chondrocytes to IL-1 in this dose range has been used to study the effects of a catabolic stimulus on the cartilage matrix and its ability to repair.

In cartilage explant cultures, the response of ankle chondrocytes to IL-1b at concentrations of 1e250 pg/ml was significantly different from that of knee chondrocytes (Fig. 8), demonstrating a reduced response by ankle chondrocytes to catabolic stimulation compared to knee chondrocytes[31]. While both knee and ankle chondrocytes responded to IL-1 by decreasing ^{35}S-sulfate incorporation into glycosaminoglycans in a dose-dependent manner, the dose at which the knee chondrocytes responded was lower than that for the ankle chondrocytes. At the lowest IL-1 doses tested, 0.1 and 0.5 pg/ml, glycosaminoglycan synthesis was unaffected in both knee and ankle chondrocytes. However, at an IL-1 dose of 1 pg/ml, glycosaminoglycan synthesis was reduced by 67% in the knee, but the ankle chondrocytes were not affected by a similar reduction until the IL-1 dose was 5 pg/ml. Between IL-1 doses of 5 and 250 pg/ml, there were significant differences in the

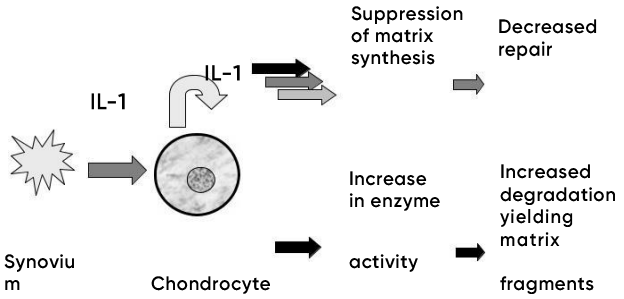

Fig. 7. Diagrammatic representation of the influence of IL-1 on the chondrocyte. The chondrocyte responds to IL-1 either from the synovium or from chondrocytes themselves. In human cartilage the primary response of the chondrocytes is to suppress synthesis of matrix components at low levels of IL-1; at higher levels of IL-1 enzyme activity is elevated, shifting the metabolic balance between anabolism and catabolism in favor of matrix degradation. Both results can be deleterious to the matrix, whether by decreasing repair or increasing degradation. OA may be considered a disorder of cartilage matrix metabolism with the superimposition of in-termittent inflammatory episodes.

suppression of glycosaminoglycan synthesis by both knee and ankle chondrocytes. At the highest IL-1 concentrations tested (500e1000 pg/ml) there was no longer a significant difference in the suppression of glycosaminoglycan synthesis between knee and ankle; the synthesis in both was reduced to that of 10% of the control.

The differences in response to catabolic stimulation between knee and ankle chondrocytes were maintained when the chondrocytes were released from their native matrix and cultured in alginate beads. The IC_{50} for decreased glycosaminoglycan synthesis by knee chondrocytes in alginate was 11.8 pg/ml and was significantly different from that of the ankle, which was 56.1 pg/ml[39]. Both of these values are similar to the IC_{50} found, respectively, for knee and ankle cartilage explants. The data showing that both knee and ankle chondrocytes maintain differences in response to increasing concentrations of IL-1b support our hypothesis that ankle chondrocytes

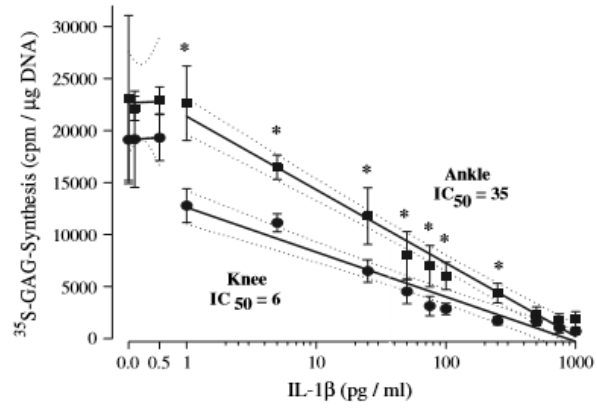

Fig. 8. The effect of interleukin-1b on proteoglycan (PG) synthesis. The effect of IL-1b on proteoglycan synthesis was evaluated by ^{35}S-incorporation into GAG as cpm per mg DNA. The results (mean G S.D.) are from matched pairs of knee (C) and ankle (–) cartilages of six different donors. Differences were considered significant at P ! 0.05 and are marked with an asterisk (). The IC_{50} for inhibition in the explant cultures of knee and ankle cartilages are indicated. Reprinted from Eger et al.[31] with
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are less responsive to catabolic stimulation, at least with regard to decreasing proteoglycan synthesis. These differences in response to IL-1 may have been caused by either the number or types of IL-1 receptors[42]. The chondrocytes of the superficial zone are more responsive to IL-1 than are cells from the deeper cartilage. This difference may result from the higher number of receptors for IL-1 on chondrocytes from the articular surface than on those from the deep tissue. It is noteworthy that the IL-1 receptor antagonist protein could completely block the IL-1 induced inhibition of proteoglycan synthesis in cells from the ankle joint, but was only partially effective in knee cartilage cells.

Following injurious compression, knee cartilage, but not ankle cartilage, responded to treatment with IL-1[30]. When the cartilage was injured and then exposed to IL-1, there was a synergistic increased loss of glycosaminoglycan in the knee. Unlike the results from knee cartilage, in ankle cartilage from the same donor there was no statistically significant interaction between injury and IL-1 treatment. These data demonstrate a synergistic effect of cytokines and cartilage injury found in the adult human knee but not the ankle, leading to the hypothesis that the interaction between joint injury and cytokines may be an underlying difference in the progression to OA of knee and ankle cartilage after injury.

RESPONSE TO MATRIX FRAGMENTS

Fragments of matrix components, such as fibronectin and collagen, can have biological activity by activating pathways that are not part of the native molecule's normal function[43]. A 29 kDa fragment from the amino terminal of fibronectin has been shown to modulate proteoglycan synthesis at low doses and degradation at high doses[44,45]. This fragment, which can be generated by MMP-3 or other catabolic proteinases, is elevated in OA synovial fluid and carti-lage[46,47]. An injection of the 29 kDa fibronectin fragment (Fn-f) into the rabbit knee joint causes severe cartilage damage with characteristics of OA[48].

When the Fn-f were incubated with matched pairs of knee and ankle cartilages, both anti-anabolic as well as catabolic pathways were activated[33,49]. Proteoglycan synthesis was reduced in a dose-dependent manner by both knee and ankle chondrocytes; however, just as with the response to IL-1, there was a difference in the concentration at which proteoglycan synthesis was significantly reduced by Fn-f. In the knee, 1 nM Fn-f significantly suppressed proteoglycan synthesis, while in the ankle, 100 nM was required. There was also a significant difference in the catabolic response of knee and ankle chondrocytes to stimulation by the 29 kDa Fn-f. There was greater proteoglycan loss and an increased activity of aggrecanase in the knee compared with the ankle; the ankle cartilage was not damaged even after 28 days in culture. The knee cartilage showed a significant loss of 30e50% of its proteoglycan as early as day 7. When the rate of degradation, measured as proteoglycan loss to the media during 7 days of explant culture, was determined, the rates for the knee and ankle were nearly identical. In the presence of the 29 kDa Fn-f, the degradation rates significantly increased to 0.68 G 0.28 mg proteoglycan/mg cartilage/day for knee cartilage and 0.58 G 0.14 mg pro-teoglycan/mg cartilage/day for ankle cartilage. In addition, the 29 kDa Fn-f significantly decreased the half-life of ^{35}S-labeled proteoglycan by 1.87-fold in the knee and 2.36-fold in the ankle, both compared to the control.

While the influence of Fn-f has primarily focused on proteoglycan regulation, studies of type II collagen fragments have focused on collagen synthesis. It was previously thought that adult human cartilage no longer ynthesized type II collagen[50,51]; however, it has recently been shown that collagen synthesis evaluated by mRNA and the CPII continues in articular cartilage, albeit at low levels[18]. Collagen is also continuously turned over through-out life as well[18], such that collagen fragments accumulate in the normal matrix at a concentration of 1e4 mg/g wet weight of the cartilage; OA cartilages contain between 7 and 17 mg/g wet weight[52]. Incubation of knee and ankle explants with collagen fragments for 21 days results in a significant loss of glycosaminoglycans as well as collagen from the explants; however, there were no significant differences in the loss between knee and ankle[52].

ATTEMPTED REPAIR

Another reason for the lack of damage progression in ankle cartilage may be that ankle chondrocytes, which are more responsive to anabolic agents than knee chondrocytes, are thus able to repair early cartilage lesions. The anabolic factor osteogenic protein-1 (OP-1, also known as bone morphogenetic protein-7) caused a marked stimulation of proteoglycan and collagen synthesis (mostly aggrecan and type II collagen) in human articular chondrocytes. OP-1 had a much more potent anabolic effect compared to other factors including TGF-1b, activin A, and IGF-1[53]. When OP-1 was tested in combination with low concentrations of IL-1, OP-1 was able to overcome the inhibitory effect of IL-1 on aggrecan synthesis. When knee and ankle explants were first incubated with IL-1b and then allowed to rebound without IL-1b, the synthesis of proteoglycans was significantly elevated by ankle chondrocytes within 5 days; knee chondrocytes were unable to significantly increase synthesis even after 8 days. In alginate beads no differences were found in the response of either knee or ankle chondrocytes to a monoclonal anti-OP-1 neutralizing antibody that suppressed proteoglycan synthe-sis and endogenous OP-1 content[54].

Differences in knee and ankle cartilage response to degenerative changes

In an attempt to compare the knee and ankle in vivo response to damage, we analyzed markers of synthesis and degradation in cartilage from joints that were Grade 0 (normal) and Grade 2 (early lesions). The results indicate a net anabolic response in the ankle cartilage lesion and a net catabolic response in knee cartilage lesions[55]. In ankle cartilage lesions, there was an upregulation of the markers of collagen synthesis and of proteoglycan synthe-sis which were downregulated in the knee cartilage lesions. In lesions of knee cartilage, but not ankle cartilage, there was a five-fold upregulation of collagen degradation markers. Compared to the ankle, there was a 24-fold increase in cleavage epitopes compared to denaturation epitopes in knee cartilage lesions. The upregulation of matrix turnover that was seen in early cartilage lesions of the ankle would appear to represent an attempt to repair the damaged matrix. The increase in collagen synthesis and aggrecan turnover seen in ankle lesions was absent from the knee lesions. Instead, there was an increase in type II collagen cleavage. Taken together with the differences in collagen denaturation, these changes point to the stimula-tion of matrix assembly during early lesion development in ankle cartilage and of degradation of the matrix in knee

cartilage. The result is a fundamental difference in matrix turnover within lesions in ankle and knee cartilage. The increase in type II collagen cleavage in early lesions of knee cartilage, but not in ankle cartilage, suggests an early predisposition to degenerative pathology in the knee, while in the ankle the early emphasis is on repair.

Response of subchondral bone to degenerative changes in cartilage

OA is characterized by both articular cartilage degeneration and subchondral bone changes; early degenerative changes in the cartilages of the knee, hip, and finger joints with progression to OA show increased subchondral bone density[56]. We therefore investigated whether the degree of degeneration of ankle cartilage (mild or moderate) corre-lates with an elevated bone density in the ankle[57]. Using peripheral quantitative computed tomography, we found that even moderate degeneration of the articular cartilage of the ankle is not accompanied by an increase in local bone density, but rather shows an associated decrease. In the ankle, cartilage degeneration appears to precede thicken-ing of the subchondral bone. Because the ankle joint is generally not affected by progressive OA, the lack of association between increased bone density and cartilage degeneration would appear to support the idea that progressive degeneration of the cartilage requires bone involvement.

Conclusions

Our studies comparing knees and ankles have shown that there are differences not only in the cartilage and subchondral bone but also in the chondrocytes themselves, which may contribute to degeneration in the knee and repair in the ankle (Table III). The accumulation of this data has been possible through collaboration with the Gift of Hope Organ and Tissue Donor Network and continuous support through a grant from NIH for a SCOR in OA. The studies have been conducted not only by intramural investigators but also by a number of extramural investigators who have contributed their expertise and unique techniques and reagents to compare knee and ankle cartilages as well as bone. The success of these studies may be attributed to the fact that we have been able to study normal knee and ankles from the ipsilateral limb of a large number of adult donors. Each of these studies has taken 2 to 3 years to complete and, thus, has proceeded at a slower pace than the average successful research project.

Our most convincing data were obtained from experi ments with cartilage explants where the chondrocytes remained in their accumulated native matrix. The pro-teoglycan content of the extracellular matrix is significantly higher in ankle cartilage than in knee cartilage. The higher proteoglycan content, along with lower water content, provide an increased stiffness and lower hydraulic perme-ability to ankle cartilage. The result is a higher compressive stiffness that could protect ankle cartilage from continuous microtrauma. The lack of a synergistic response of ankle chondrocytes to injurious compression and IL-1 suggests that, even with traumatic injury, ankle cartilage is more resistant to the progression of degeneration. Together, these data show that the extracellular matrix plays a significant role in protecting the cartilage in the ankle. The extracellular matrix also plays a role in maintaining the differences between knee and ankle cartilage. In a number of our studies, the chondrocytes were first

Table III
Summary of knee and ankle differences

Feature	Knee	Ankle
Joint stability	Relatively unstable	Highly stable
	Non-congruent	Highly congruent
Joint motion	Flexion/extension	Flexion/extension
	Rotation	
Cartilage		
Cellularity	Same	Same
Cartilage thickness	2e6 mm	1e1.5 mm
Superficial chondrons	Single cells	Clusters of 2e4 cells
Sulfated glycosaminoglycan content	Lower	Higher
Water content	Higher	Lower
Collagen content	Same	Same
Dynamic stiffness	Lower	Higher
Hydraulic permeability	Higher	Lower
Peak stress with 65% final strain	11 MPa	16 MPa
Glycosaminoglycan synthesis		
In explants	Lower	Higher
In alginate	Same	Same
Proteoglycan half-life	22.68 days	16.58 days
Protein synthesis	Lower	Higher
IC_{50} for IL-1 reduction of proteoglycan synthesis		
In alginate	11 pg/ml	56 pg/ml
In explants	6 pg/ml	35 pg/ml
Influence of Fn-fs on		
Proteoglycan synthesis (anti-anabolic)	Low dose (1 nM)	High dose (100 nM)
Proteoglycan loss (catabolic)	Significant at 7 days	Not significant after 28 days
Attempted repair (Response to anabolic factors following catabolic stimulation)	No significant rebound	Significant rebound
Response to degeneration	Upregulation of collagen degradation	Upregulation of matrix synthesis

released from their native matrix and allowed to reform a new matrix in either alginate or agarose. In the newly formed matrix, there were no longer significant differences in response to compression, nor were the differences in proteoglycan content or synthesis maintained. However, there were differences that were not lost, such as the dose response to IL-1, suggesting that some of these differences were programmed into the chondrocytes themselves re-gardless of their extracellular matrix, just as was previously shown for superficial and deep chondrocytes. Differences in response to IL-1 may be due to differences in either the number or types of IL-1 receptors that are maintained in both superficial and deep chondrocytes taken from knee and ankle.

Ankle chondrocytes display a decreased response to not only IL-1 but also to other catabolic factors, such as Fn-f in explant cultures. In addition, ankle chondrocytes have an increased response to anabolic agents, such as OP-1. These data are supported by our analyses of markers of degradation and synthesis in vivo. Damaged (Grade 2) ankle cartilage contains higher levels of CPII, indicative of collagen synthesis, and 846-epitope, indicative of pro-teoglycan synthesis, accompanied by lower levels of degradation neoepitopes. Although degeneration occurs in ankle cartilage, its progression may be slower compared to the knee due to the continuing attempts to repair.

The ankle appears to provide an in vivo model for studying reparative response mechanisms that are not present in the knee. Our current data suggest that there is not a single property, but numerous subtle differences between the cartilages, as well as the bone, from the two joints, which could help protect the ankle cartilage from progressive degenerative changes. By understanding how knee and ankle cartilages differ from one another, we can begin to identify factors active in the early stages of cartilage damage that may precede OA. Our ultimate goal in OA research is to develop the means of blocking the progression of the disease process and to reverse its effects. One method of reversing the effects of early disease processes is to decrease the response of chondrocytes to catabolic factors and to stimulate the chondrocytes to rebuild their matrix. Effectively, simulating the characteristics of ankle chondrocytes in different joints should facilitate the development of therapeutic strategies for the early detection and prevention of OA. The ankle may provide a model for studying reparative response mecha-nisms that are absent or diminished in the knee.

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Notes

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Notes

Are joints designed to protect us from injuries?

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