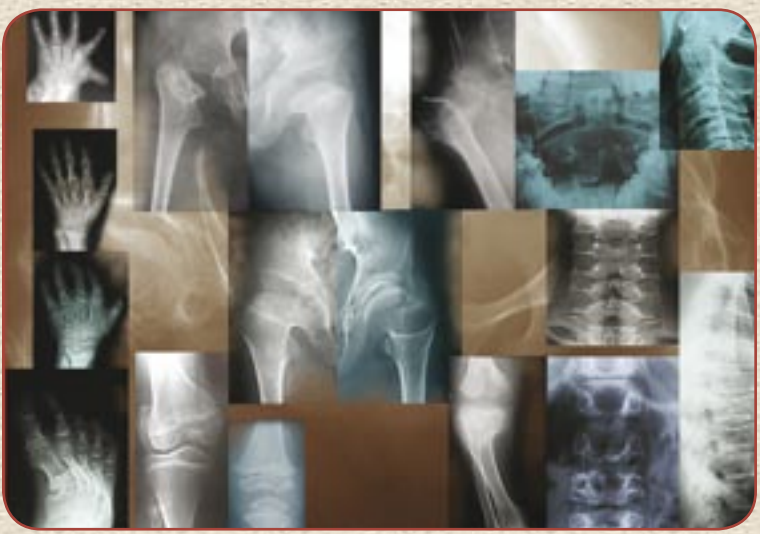
# Pohybové ústroji

## Pokroky ve výzkumu, diagnostice a terapii



Vydává Společnost pro pojivové tkáně ČLS J. E. Purkyně
Ambulantní centrum pro vady pohybového aparátu
Katedra antropologie a genetiky člověka PřF UK v Praze
Odborná společnost ortopedicko-protetická ČLS J. E. Purkyně

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# LOCOMOTOR SYSTEM
**Advances in Research, Diagnostics and Therapy**

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The journal has an interdisciplinary character which gives possibilities for complex aproach to the problematics of locomotor system. The journal belongs to clinical, preclinical and theoretical medical branches which connect various up-to-date results and discoveries concerned with locomotor system.

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# POHYBOVÉ ÚSTROJÍ,
# 14, 2007, č. 1+2

Pokroky ve výzkumu, diagnostice
a terapii


## OBSAH




# LOCOMOTOR SYSTEM
# 14, 2007, No. 1+2

Advances in Research, Diagnostics
and Therapy


## CONTENT

**Vážení čtenáři, autoři a inzerenti,**

rádi bychom Vám poděkovali za Vaši pomoc při tvorbě mezioborového odborného časopisu *„Pohybové ústrojí - pokroky ve výzkumu, diagnostice a terapii“*.

Na jaře roku 2007 Vám předkládáme dvě dvojčísla časopisu, a to 3 + 4/2006 a 1+2/2007, kde jsou v suplementu publikovány práce (in extenso) z „The 8th Lublin- Prague-Sydney Symposia“, které se koná 20.-21. 4.2007 v Lublinu díky obětavé organizaci pana prof. Tomasze Karskiho, M.D., PhD., člena redakční rady časopisu.

Rok 2007 je pro členy redakční rady výjimečný, protože se po mnoha letech podařilo vyrovnat zpoždění ve vydávání časopisu, což je zásluhou jak členů redakční rady, tak všech čtyř spoluvydavatelů. Za vysokou odbornou grafickou a technickou úroveň děkujeme odpovědnému redaktorovi časopisu panu Ing. P. Lorencovi.

V roce 2007 plánujeme dvoudenní symposium The 9th Prague-Sydney Symposium & 12th Kubát´s Podiatric day *„News in Diagnostics and Comprehensive Treatment of Locomotor Defects“* s mezinárodní účastí, které se bude konat v Lékařském domě (Sokolská 31, 120 26 Praha 2) 19.–20. 10. 2007.

I nadále předmětem a hlavním posláním časopisu je publikování prací vycházejících z výzkumu pojivových tkání, práce orientované na biochemickou, morfologickou, genetickou a molekulární diagnostiku, kostní metabolismus u vrozených poruch i získaných vad. Dále klinické práce, týkající se symptomatické léčby metabolických kostních chorob, osteoporózy, osteo/spondyloartrózy, kostních dysplazií, končetinových anomálií, dismorfických vad pohybového aparátu a genetických syndromů, ale i jiných chorob, které ve svých důsledcích negativně ovlivňují pohybové ústrojí v průběhu lidského života. Pozornost patří pracím z oblasti biomechaniky na všech úrovních poznání, a to neuroadaptivním změnám skeletu, řízené remodelaci pojivových tkání v závislosti na léčebných metodách (kalciotropní léky, rehabilitace, ortoticko-protetické a operační léčení), studiím muskuloskeletálních a neuronálních interakcí, v neposlední řadě sdělením antropologickým, paleopatologickým a pod. Perspektivně bude věnován prostor na stránkách časopisu pracím z oblasti sekundární osteoporózy. Ceníme si především interdisciplinárně zaměřených příspěvků. V anglickém jazyce jsou publikovány práce zahraničních i našich autorů. Cenným doplněním obsahu časopisu jsou zprávy ze sjezdů a konferencí. V rubrice zprávy zveřejňujeme oznámení o životním výročí členů RR, prioritních pozorováních, ze studijních a poznávacích cest aj.

Jako každoročně uvádíme směrnice pro autory příspěvků. Původní práce a kasuistiky doporučujeme publikovat v angličtině s cílem zvýšit zájem o náš časopis i ve státech EU. Souhrny prací publikovaných v časopisu jsou excerpovány v EMBASE / Excerpta Medica, a proto doporučujeme autorům, aby využili této příležitosti a psali co nejvýstižněji anglické souhrny s klíčovými slovy.

Do redakční rady byl přijat pan MUDr. Pavel Novosad, člen SMOS ČLS JEP a zakladatel Osteologické Akademie Zlín ČLS JEP. Těšíme se na plodnou tvůrčí spolupráci v roce 2007 i dalších letech, ke které vyzýváme všechny čtenáře.

Redakční rada

# OBRÁZEK NA TITULNÍ STRANĚ ČASOPISU DEMONSTRUJE

Obrázek na titulní straně časopisu demonstruje charakteristické RTG příznaky **diastrofické dysplazie (DD)**, a to: oploštělé epifýzy, opoždění osifikace epifýz hlavic femurů, poloměsíčitý tvar epifyzárních osifikačních center, neúplná osifikace laterální poloviny distální epifýzy femuru. Krčky femurů jsou krátké a široké, široké jsou všechny metafýzy dlouhých kostí, které jsou významně zkrácené. Nepravidelné deformity a zkrácení všech metakarpů, metatarsů a článků prstů, 1. metakarp bývá u dětí oválný. Ploché a široké epifýzy metakarpů mohou být jediným příznakem u mírných forem DD. U dětí bývají deltovité deformity distálních metafýz femurů a radií. Na páteři často progreduje dorsolumbální kyfoskolióza a krční kyfóza. Obratlová těla jsou nepravidelně deformována a jsou relativně dobře vyvinutá. Platyspondylie nevylučuje však diagnózu DD. V dolní lumbální krajině bývá mírné zúžení interpedikulární vzdálenosti.

Na obrázku jsou vyobrazeny **typické radiografické dysplastické změny** pozorované **na ruce, noze, kyčelních a kolenních kloubech i páteři** u pacientů s DD v různém věku, kteří jsou nebo byli léčeni v Ambulantním centru pro vady pohybového aparátu v Praze.

## Ruka

Nepravidelné zkrácení a deformity metakarpů a falang s rozšířením metafýz a plochými epifýzami jsou patrny v na snímcích dětí i dospělých. Nalevo obrázku jsou pod sebou RTG levé ruky, nahoře na RTG ruky ve věku 2,5 roku je patrna dislokace metakarpofalangeálního kloubu palce, oválný deltovitý tvar 1. metakarpu a výrazné zúžení proximálních interfalangeálních kloubů, které svědčí pro symfalangismu. Níže umístěné obrázky –11 a 9 let – ukazují velmi ploché a nepravidelné epifýzy radia a ulny.

## Páteř

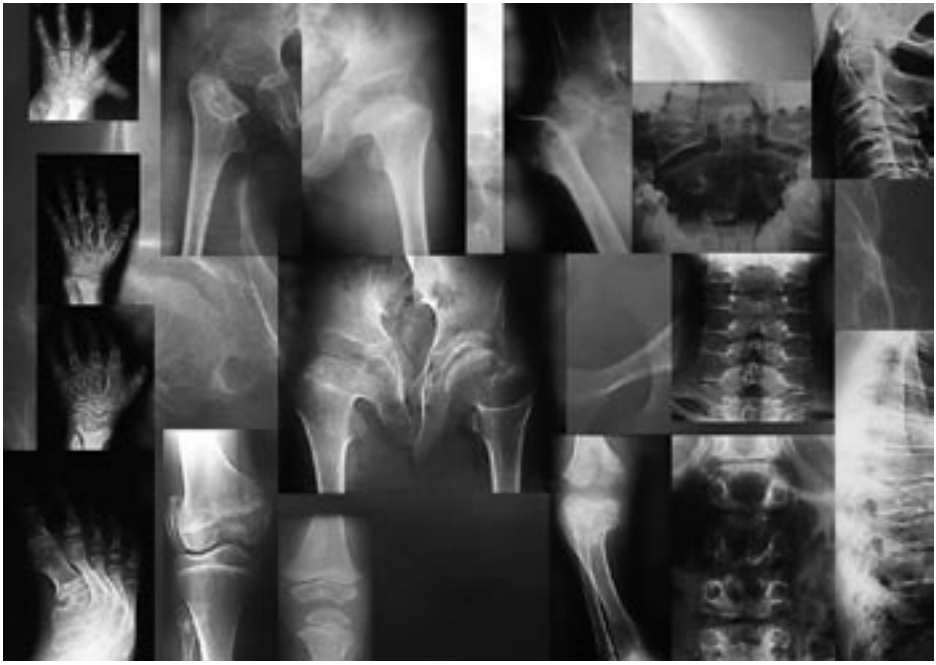
Vlevo dole je RTG přednoží 9letého pacienta, kde je výrazné equinovarosní postavení, metatarsy jsou krátké s širokými metafýzami, zobrazené epifýzy jsou velmi ploché.

## Kyčle

Nahoře a uprostřed obrázku jsou kyčelní klouby 4 pacientů ve věku – zleva 2,5; 6,5 a 5,5 roku, uprostřed zleva 9 a 11 let. Krčky jsou krátké a široké, epifýzy značně oploštělé, s věkem progredují abdukční a flekční kontraktury.

## Kolena

Dole na obrázku je RTG kolen 3 pacientů ve věku – zleva 12,5 a 2,5 roku, kde je mírné oploštění epifýz, na obrázku vlevo je laterální luxace čéšky, na obrázku vpravo – 9 let – je těžká deformita kolenního kloubu i bérce, který je varosní a rotován dovnitř.



**Páteř**

V pravé části obrázku nahoře na snímku v transorální (13,5 roku) a bočné (24 let) projekci je dobře vytvořený dens epistrophei, mírné oploštění obratlových těl s ventrálními osteofyty. Vpravo uprostřed je na snímku krční páteře v předozadní projekci –11 let – zobrazena spina bifida occulta dolních krčních obratlů, vpravo dole je ukázáno mírné zúžení páteřního kanálu bederní páteře – 6,5 roku, na pravém okraji obrázku dole je ne zcela pro diagnózu typický obraz platyspondylie dorsolumbální páteře se známkami předčasné spondylózy – 20 let.

**Dědičnost**

Dědičnost je autosomálně recesivní (AR) s velmi širokou variabilitou exprese postižení. Prenatální diagnostika je možná v 16. týdnu gravidity na základě zjištění krátkých končetin, pedes equinovari, ulnární deviace rukou a stopařských palců. Z biopsie choriových klků lze prokázat mutace v genu sulfátového transportéru diastrofické dysplazie (DTDST). Mutace postihují různé domény DTDST genu, což vysvětluje širokou variabilitu exprese fenotypu.

Mutace znemožňuje buněčnou inkorporaci sulfátu a nedostatečná sulfatace proteoglykanů vede k narušení tvorby matrix chrupavky.

## Klinická symptomatologie

Krátká postava a krátké končetiny, mnohočetné kloubní kontraktury zvláště ramenních, loketních, kyčelních a interfalangeálních kloubů. Hypermobilní vysoko nasedající palce rukou (tzv. stopařský palec). Chybění volární ohybové rýhy proximálních interfalangeálních kloubů prstů rukou označuje fibrosní někdy i kostěný symfalangismus. Pedes equinovari s větším meziprstním prostorem mezi 1. a 2. prstem. Nepravidelně pseudocystické zduření ušních boltců (patrné od prvních dnů do 3 měsíců věku) později květákovitá deformita ušních boltců. Rozštěp patra bývá zjištěn u 50 % případů. U většiny dětí progreduje kyfoskolióza.

## Průběh

Perinatální a kojenecká úmrtnost je zvýšená. Nevzniknou-li vážné komplikace z důvodů deformit páteře, je životní prognóza normální. Progrese cervikální kyfózy může vést ke kompresi míchy s rozvojem kvadruplegie a letálním koncem Generalizované postižení mesenchymu vede v období růstu k progresi kyfoskoliózy páteře, kontraktur a těžkým equinovarosním deformitám nohou, které vzdorují ortopedickému léčení – kontraktury recidivují. V průběhu růstu je třeba individuálně kombinovat konzervativní a operační léčení kontraktur a deformit dlouhých kostí. Míšní komprese a progrese krční kyfózy je indikací k operačnímu léčení v raném věku. Předčasná osteoartróza kyčelních kloubů vzniká v důsledku těžké epifyzární dysplazie a progredujících kontraktur s růstem. V indikovaných případech se řeší po skončení růstu kloubní náhradou. Z dentálních anomálií jsou nejčastější hypodoncie, komprese zubů a malokluse. Výška dospělých mužů je v rozmezí 114–158 cm (průměr 136 cm) a 98–143 cm u žen (s průměrem 129 cm).

*Pro kostní dysplazie obecně platí, že pro určení diagnózy je diagnosticky cenné hodnocení dysplastických změn epifýz, metafýz a obratlů na RTG snímcích zhotovených v období růstu. Dysplastické změny kyčelních kloubů a celého skeletu u pacientů s DD jsou pro potvrzení diagnózy typické od narození do dospělosti.*

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# VLIV JÁCHYMOVSKÉ RADONOVÉ LÉČBY NA VYBRANÉ METABOLICKÉ MARKERY U PACIENTŮ INDIKOVANÝCH K LÁZEŇSKÉ LÉČBĚ POHYBOVÉHO APARÁTU*)

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[1] Léčebné lázně Jáchymov, a.s.

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[3] Nemocnice České Budějovice, a.s.

## SOUHRN

Na vybraném vzorku pacientů s onemocněním pohybového aparátu jsou zhodnoceny již 100 let známé positivní výsledky radonové lázeňské léčby v jáchymovských lázních. Objektivizovaný dotazník vyjadřuje u všech pacientů zlepšení kvality zdraví a pohybu všech pacientů. Laboratorně je doložen pokles sérového C-reaktivního proteinu a molondialdehydu za 3 měsíce po skončení lázeňských procedur. Sérový kortizol a fagocytární aktivita leukocytů C byla zvýšena v období ukončení lázeňské léčby a její normalizace nastala rovněž do 3 měsíců po skončení. Ostatní sledované laboratorní markery (orosomukoid, haptoglobin, alfa-1-antitrypsin a fagocytární aktivita leukocytů N nevykazovaly signifikantní změny v průběhu lázeňské léčby ani po jejím skončení.

**Klíčová slova:** radonová léčba, pohybový aparát, klinické a laboratorní markery (CRP, malondialdehyd, kortizon, fagocytární aktivita), jáchymovské lázně ČR

## SUMMARY

100 years known positive effect of Jachymov spa treatment is evaluated at representative sample of patients suffering from disorders of locomotor apparatus.

*) Předneseno na Zasedání Evropského svazu radonových lázní (ARGE) Schlema (NSR),2005 a na Konferenci Odb. společnosti rehabilitace a fysikální mediciny Jáchymov, 2005 při příležitosti 100letého výročí založení lázní Jáchymov.

Jachymov spa treatment leads to decreasing of oxidative stress. In selected form, there was proved decreasing of this intensity by 14 % from starting values immediately after the end of treatment and by 21 % from starting values in term of 3 months after treatment. This decreasing of oxidative stress intensity is statistically relevant on 1% level of significance.

Jachymov spa treatment leads to decreasing of present inflammation intensity. In selected form, there was proved average decreasing values of inflammation markers by 5.4 % from starting values immediately after the end of treatment and by 5.5 % from starting values in term of 3 months after treatment. Decreasing of one from significant markers – orosomukoin – was statistically relevant on 5% level of significance. This decreasing was moreover apparent and statistically relevant on 5% level of significance even 3 months after the end of Jachymov spa treatment.

Jachymov spa treatment leads to increasing of average levels of plasmatic cortisol on 116 % of starting values. This proved increasing of levels of plasmatic cortisol was statistically relevant on 1 % level of significance.

Jachymov spa treatment leads to increasing of cell immunity, expressed as fagocytal ability of leukocytes, by 5 % of starting values. This phenomenon was in slightly apparent even 3 months after treatment.

Jachymov radon water bathes increase statistically significantly cell immunity even by health patients by 19 % according to starting values. This increasing of fagocytal ability of leukocytes was statistically relevant on 1% level of significance.

Jachymov spa treatment leads to increasing of life quality contingent on health. (Health Related Quality of Life concept) in all eight domains of life quality.

The treatment improves physical functions, physical restraints of roles, emotional restraints of roles, physical and emotional restriction of social functions, it affects pain sensibility, it improves stage of mental health, it increases energy/vitality and improves the whole perception of respective health. In domains of physical and emotional restriction of social functions and mental health are these improvements statistically evidential on 5 % level of significance.

**Key words:** Radon treatment, locomotor apparatus, clinical and laboratory markers (CRP, malondialdehyd, cortisol, fagocytal activity), Jachymov Spa Czech Republic

# ÚVOD

Opakovaně bylo prokázáno a pozorováno, že nízké dávky ionizujícího záření v množství 0,5–1,2 Gy vykazují prokazatelnou protizánětlivou účinnost (**1, 2, 10, 11, 15, 16, 17**). Pro mechanismus účinku ionizujícího záření na ústup klinických příznaků však dosud není jednoznačně vysvětlen, molekulární účinky podrobně popsali Nardet, Rödl a další (**2, 4, 6, 7, 13, 15**). Zřejmě dochází ke zvýšení protizánětlivých a snížení prozánětlivých mediátorů (**4, 8**). In vitro byla prokázána snížená adheze lymfocytů na endotheliální buňky a ostatní do současnosti známé radiobiologické účinky na lidský organismus prezentovali ve svých přednáškách Prof. MUDr. Klenner a ze zahraničních autorů Deetjen, Falkenbach, Kaul, Prise, Rödel, Trott aj. Zevrubně jsou

positivní účinky spolu s účelnými indikacemi popsány jak v posledním sborníku „Radon als Heilmittel (2005)“ tak v učebnici Vnitřního lékařství (**1, 2, 3, 5, 9, 12**).

K prvým významným aktivitám lázeňským v Jáchymově přispělo šťastné setkání dvou významných osobností na přelomu 19. a 20. století: báňského inženýra Josef Sťepa a okresního lékaře MUDr. Gottlieba. Tito pánové dali první podnět k tomu, aby prameny z podzemí byly využity k léčebným účelům. A tak byly zřízeny první „lázničky“ v domě místního pekaře kam radioaktivní voda byla donášena v zakrytých dřevěných putnách. Už tehdy byly příznivé účinky „radonových koupelí“ lékařsky prokazatelné a nezpochybnitelné (**7**). Pro vznik jáchymovských lázní je třeba uvést základní historická data jakými je objev radioaktivity A. Beckerelem v r. 1896; objev radioaktivních prvků manželi Curiovými v r. 1898 a poznatky prvních biologických projevů radioaktivního záření, které popsal P. Curie 1903. Radioaktivitu jáchymovských vod popsal v r. 1905 H. Mach a už v r. 1906 byly provozovány radonové koupele a tedy založeny v Jáchymově první radonové koupele na světě. V roce 1910 byl zahájen léčebný provoz lázní Agricola, v r. 1912 byla otevřen Radium Palace a postupně další léčebny. Během 100leté historie jáchymovských lázní zdejší zařízení navštívilo mnoho set tisíc pacientů z celého světa. Mezi prominentními návštěvníky byli např. Prof. M. Curie Sklodowska, prezidenti T. G. Masaryk, Dr. Eduard Beneš a řada prominentních umělců a básníků: A. Jirásek, O. Nedbal, R. Strauss, F. Saljapin, egyptský král Faud a další monarchové a politici.

**Cílem našeho sdělení je:**

a) objektivizovat vliv radonové léčby na léčbu pacientů s onemocněním pohybového aparátu pomocí vybraných laboratorních markerů před zahájením, bezprostředně po skončení lázeňské léčby a konečně 3 měsíce po jejím ukončení;
b) zkorelovat výsledky objektivních měření se subjektivním hodnocení odléčených pacientů

## VÝBĚR PACIENTU PRO LÁZEŇSKOU LÉČBU A METODIKA

Soubor 111 pacientů byl v době od 1. 8. 2003 do 25. 8. 2004 sestaven náhodným výběrem z pojištěnců odesílaných do LL Jáchymov dle platného indikačního seznamu 58/97 Sb. v indikační skupině VII s těmito diagnozami: onemocnění pohybového aparátu (PA) zánětlivá (revmatoidní arthritis a ostatní revmatologická onemocnění); spondylitis ankylosansm.Bechtěrev; degenerativní onemocnění kloubů a páteře; stavy po operacích a úrazech PA; z neurologických onemocnění pak kořenové syndromy páteře, neuritidy, polyneuritidy stavy po operacích periferního nervového systému a konečně osteoporozy. Náš soubor čítá 42 mužů s průměrným věkem 59 let (29–82) a 69 žen; prům. věk 67 let (28–82); zánětlivými onemocněními trpělo 70 pac. (69,3 %) a 40 nezánětlivými onemocnění (40,7 %).

Soubor 24 dobrovolníků sestaven ze zaměstnanců LL Jáchymov a jejich rodinných příslušníků: 22 žen a 2 mužů prům. věku 56,5 let; léčení probíhá po $^1/_2$ roce – soubor je dvojitě slepý, dvojitě maskovaný

doplněný jedním překřížením. Prakticky se děje formou 24 koupelí v pokusné vaně monitorované automatickým čipem. Pacient ani obsluhující personál není informován o kvalitě vody výběru pacienta pro hodnocení testu. Koupele se střídají v radonové a bezradonové vodě stejně ohřívané.

Odběr krve pro potřebná laboratorní stanovení markerů proveden ráno nalačno po 12 hodinách hladovění bezprostředně před zahájením léčebné kůry; dále poslední den léčebné kůry a konečně 3 měsíce po skončení léčebné kůry byli pacienti pozváni ke kontrolnímu vyšetření. Spektrum vyšetření obsahuje: stanovení malondialdehydu (MDA) v reakci s kys. 2-thiobarbiturovou; C-reaktivního proteinu (CRP) imunoturibidimetricky na analyzátoru Advia 1650 Bayer (reagencie DAKO), haptoglobin (HP) – (reagencie Siemens Diagnostics Solutions); alfa-1-antitrypsinu (A1AT) a orosomukoidu (Oro) nefelometricky na systému DADE Behring BN I I (včetně reagencií); kortizolu (KOR) elektrochemiluminiscenční imunoanalýzou (ECLIA) Roche; fagocytární aktivity leukocytů (FAG) stanoveny jednak mikroskopickým hodnocením % fagocytujících buněk po přidání standardizovaných plastikových partikulí a jednak hodnocením fagocytozy standardizovaného kmene Candida albicans.

Pro subjektivní zhodnocení zdravotního stavu pacienta byl použit „Dotazník SF-36 o kvalitě života podmíněné zdravím" v české jazykové mutaci. Jeho plný text uveden v **Tab. 3.**

Pro statistické zpracování použito Studentova t-testu; statistická významnost hodnocena při $p > 0,05$.

## METODIKA LÉČBY

Směs 4 pramenů radonové vody zajišťuje stále stejnou radioaktivitu při balneaci.Koncentrace radonu (Rn) ve vaně činí 4,3–5,5 kBg/l; teplota koupele 35–37 °C; doba trvání koupele 20 min. a následuje zábal po koupeli v délce 10 min.; frekvence koupelí 6x týdně. Pacient absolvuje v průběhu 1 lázeňské kůry minimálně 10 a maximálně 24 koupelí. Klasická jáchymovská léčba představuje 18–24 koupelí. Pokud zdravotní stav pacienta vyžaduje další opakování lázeňské kůry je aplikace možná až za 6 měsíců. K disposici je poskytovaná i ambulantní lázeňská kůra v počtu 10 koupelí celkem.

Pro hodnocení úspěšnosti léčby použit dotazník HRQol v české písemné versi SF-36 (**Tab. 3**).

## LÉČEBNÉ ZDROJE

K lázeňské léčbě jsou rutině využívány 4 přírodní léčebné prameny získávané v lokalitě dolu Svornost Jáchymov.Jejich podrobné složení uvedeno v **Tab. 1.** Fysikální podmínky v aplikovaných koupelích pro pacienty jsou podrobně uvedeny v **Tab. 2.**

Ochrana pacientů a personálu proti radiobiologické aktivitě spočívá v udržování koncentrace Rn v ovzduší balneoprovozů v koncentraci od 50 do 300 Bq/m$^3$, která je svou koncentrací srovnatelná s většinou zdravotnických budov v ČR. K udržení této koncentrace je nutná výkonná vzduchotechnika s dokonalou údržbou respektující standard ISO 9001. Čtvrtletní kontroly registrovány SUJB. Maximální roční radiobiologická dávka např. pro lázeňskou činila v r. 2004 2,01 mSv, ale průměrná roční dávka všech lázeňských činila jen 1,42 mSv.

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CROCODILE o.s.

# DOTAZNÍK SF-36
# O KVALITĚ ŽIVOTA PODMÍNĚNÉ ZDRAVÍM

**Návod:** V tomto dotazníku jsou otázky týkající se Vašeho zdraví. Vaše odpovědi nám pomohou zhodnotit, jak se cítíte a jak se Vám daří zvládat běžné činnosti.

Odpovězte na každou otázku, že vyznačíte příslušnou odpověď. Nejste-li si jisti, jak přesně odpovědět, odpovězte jak nejlépe umíte.

1. Řekl(a) byste, že Vaše zdraví je celkově:

| | (zakroužkujte jedno číslo) |
|---|---|
| Výborné | 1 |
| Velmi dobré | 2 |
| Dobré | 3 |
| Dosti dobré | 4 |
| Špatné | 5 |

2. Jak byste hodnotil(a) své zdraví se stavem před rokem?

| | (zakroužkujte jedno číslo) |
|---|---|
| Mnohem lepší než před rokem | 1 |
| Poněkud lepší než před rokem | 2 |
| Přibližně stejné jako před rokem | 3 |
| Poněkud horší než před rokem | 4 |
| Mnohem horší než před rokem | 5 |

**Tab. 3.** Dotazník SF Dotazník SF-36, Stanovení parametrů HRQoL
– Probandi I. a II. → dotazník SF-36 v české jazykové mutaci,
– Statistické vyhodnocení s použitím Studentova t-testu

**Léčebné zdroje – přírodní léčebné prameny – lokalita důl Svornost Jáchymov**

| Pramen | Aktivita | Vydatnost |
|---|---|---|
| Curie | 5,87 ± 0,7 | 0,475 ± 0,0 |
| C – 1 | 12,22 ± 1,1 | 0,722 ± 0,15 |
| Ak. Běhounek | 10,27 ± 0,8 | 5,157 ± 0,44 |
| Agricola (HJ 14)* | 17,60 ± 0,5 | 0,15 |

* Pramen navrtán v roce 2000

**Tab. 1.** Složení přírodních léčebných pramenů z lokality důl Svornost Jáchymov

**Fyzikální podmínky v aplikovaných koupelích**

| Datum | 03. 11.–30. 11. 2003 | 19. 01.–15. 02. 2004 | 03. 05.–30. 05. 2004 | 27. 09.–24. 10. 2004 |
|---|---|---|---|---|
| skupina | 1 | 2 | 3 | 4 |
| Prům aktivita Rn vody | 4,52 kBq/l | 4,30 kBq/l | 4,12kBq/l | 4,48 kBq/l |
| Prům EOAR vzduchu | 65 Bq/m³ | 58 Bq/m³ | 78 Bq/m³ | 91 Bq/m³ |
| Prům teplota vzduchu | 21,5 °C | 22 °C | 23 °C | 22 °C |

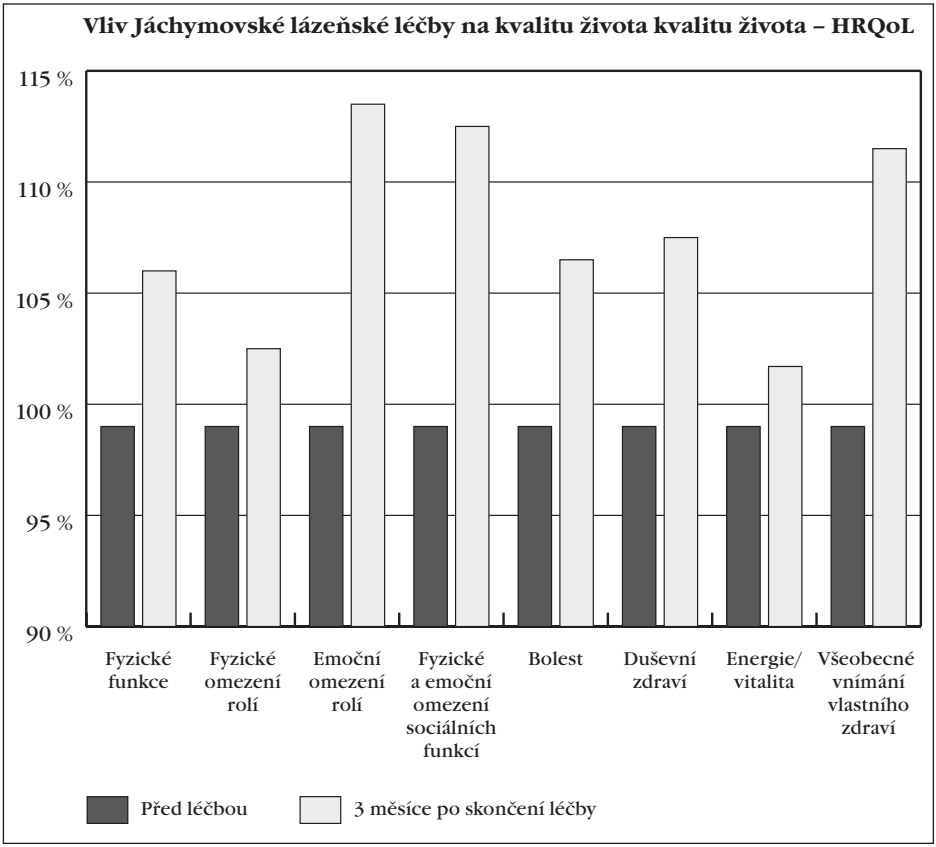
Průměrná aktivita radonové vody ve vaně 4,36 kBq/l
(rozptyl hodnot 4,09 –4,88 je vzhledem
k celkové chybě měření 15 % zanedbatelný
Efektivní dávka pacienta na jednu koupel 0,18 mSv
Dávka na kůži na jednu koupel 0,545 mGy
Efektivní dávka pacienta na 24 koupelí 4,31 mSv
Dávka na kůži na 24 koupelí 13,1 mGy
Měření probíhala 1 x týdně a monitorují čistý příjem Rnz vanové koupele na kůži probanda

**Tab. 2.** Fysikální podmínky aplikovaných koupelí

# VÝSLEDKY

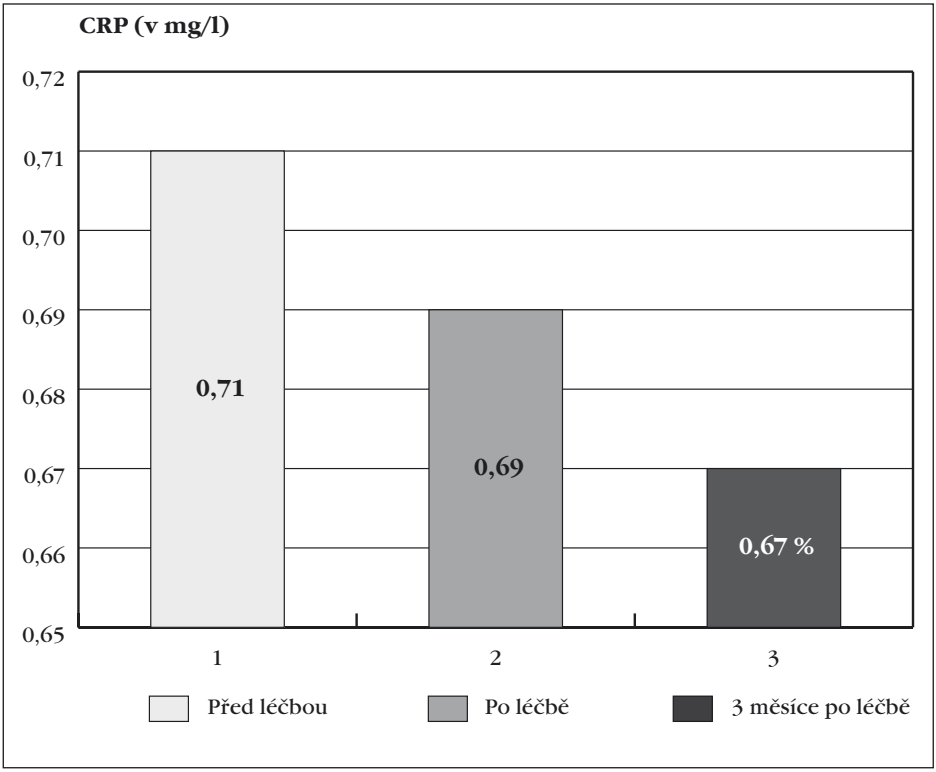
Přehledně jsou uvedena data vyhodnoceného dotazníku v **Obr. 1.** Z grafu je na prvý pohled zřejmé, že ve všech hodnocených kvalitách po lázeňské kůře došlo ke zlepšení. Jáchymovská lázeňská léčba vede ke zlepšení kvality života ve všech 8 dotazovaných doménách tj.: zlepšuje životní funkce; zlepšuje fysické a emoční omezení rolí(?); zlepšuje fysické emoční omezení sociálních funkcí; zlepšuje prožívanou bolest; zlepšuje stav duševního zdraví; zlepšuje vitalitu a celkové vnímání vlastního zdraví. Jak je možno z dotazníku vystihnout všichni pacienti nejvíce hodnotí snížení bolesti, zvýšenou fysickou i psychickou aktivitu a další funkce hodnotí individuálně podle způsobu života.

Výsledky laboratorních markerů je možno rozdělit do 3 skupin:




**Obr 1.** Vliv Jáchymovské lázeňské léčby na kvalitu života kvalitu života – HRQoL

a) prvá skupina zaznamenává výrazný pokles. Je to především výrazný a kontinuální pokles CRP hlavního zánětlivého markeru skoro o 30 % ještě za ½ roku po ukončení léčby **Obr. 2.**; dále signifikantní pokles MAD o 22 % podobného charakteru jako u předchozího vyšetření zde však jako ukazatele intenzity oxidačního stresu, **Obr. 3.**
b) druhá skupina markerů vykazuje zřetelné zvýšení po ukončení aktivní léčby před propuštěním pacienta. Týká se jak plasmatického kortizolu tak fagocytární aktivity leukocytů C, jejichž hodnoty dosahují po půl roce původních výchozích hodnot. **Obr. 4., 5., 6.**
c) třetí skupina metabolitů nedává signifikantní změny jimiž by na lázeňskou léčbu radonových koupelí reagovala. Patří sem Hb, S-1AT, Oro a Fag N. (**Obr. 7.**)

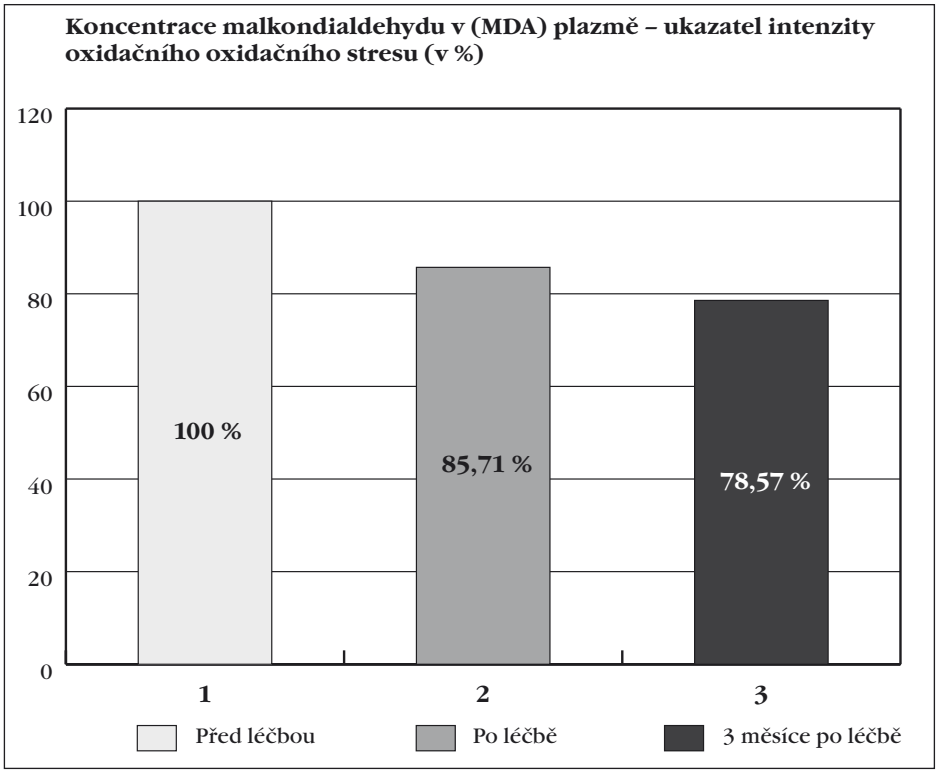



**Obr 2.** Hladina CRP před a po léčbě

## DISKUSE

Fakt že LL Jáchymov pomáhají je znám již více jak 100 let! Svědčí o tom už statisíce úspěšně odléčených pacientů. Tato sonda jen ukazuje jen účinek radonové léčby na vybraný zlomek pacientů, který jsme mohli přesněji definovat a změřit. Specifický léčebný efekt přírodních radonových vod spočívá v tom, že dochází po léčbě k velmi výraznému analgetickému efektu a zlepšení hybnosti kloubů; dále prodlužuje fázi remise u zánětlivých chorob PA. Terapeutický efekt přetrvává ještě minimálně 9 měsíců po ukončení léčebné kůry. Na rozdíl o bahenních zábalů isotermická teplota koupele a specifický mechanismus vasodilatace během koupele výrazně snižuje zatížení kardiovaskulárního aparátu při aplikaci vany. To umožňuje intenzivní koupelovou kůru i kardiakům, hypertonikům a seniorům. Tyto zásadní faktory preferují radonovou léčbu před ostatními druhy lázeňské léčby na celém světě.

Vzhledem ke složení souboru pacientů v průběhu studie nebylo prováděno náročnější laboratorní vyšetření nových specifických markerů zánětu jako např. cytokiny,




**Obr 3.** Koncentrace malkondialdehydu v (MDA) plazmě – ukazatel intenzity oxidačního oxidačního stresu (v %) před a po léčbě

interleukiny, CD 40, protože nebylo dostatečné finanční zajištění (**12**). Pokud se podaří zajistit potřebné finanční podmínky budeme v zahájené studii pokračovat.

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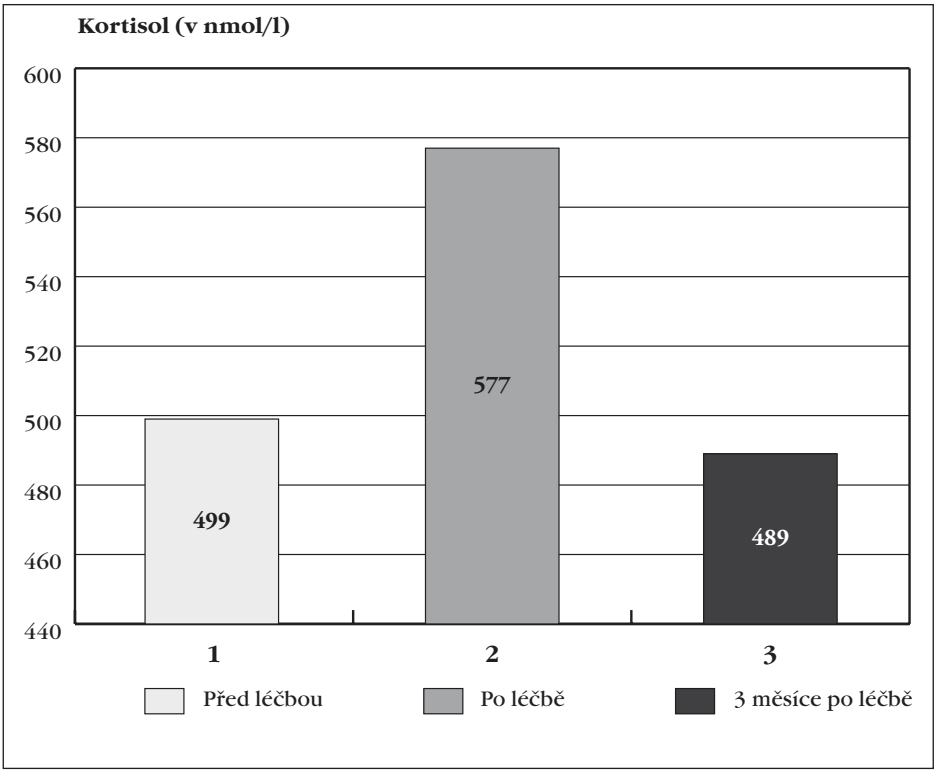


**Obr 4.** Hladiny kortisolu (v nmol/l) před a po léčbě

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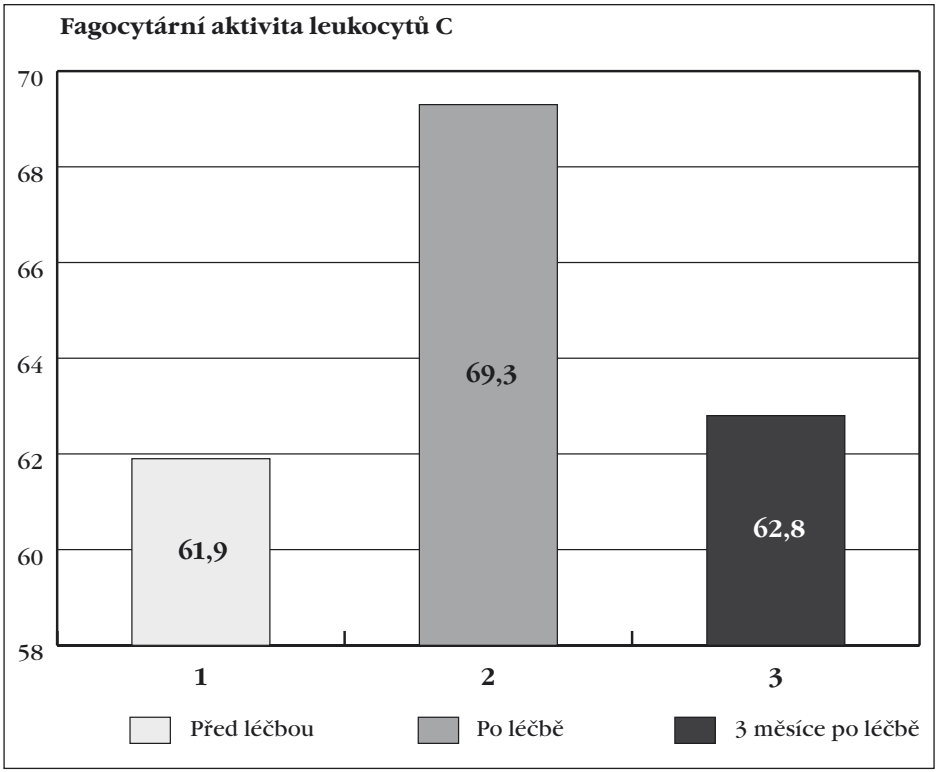


**Obr 5.** Fagocytární aktivita leukocytů C před a po léčbě

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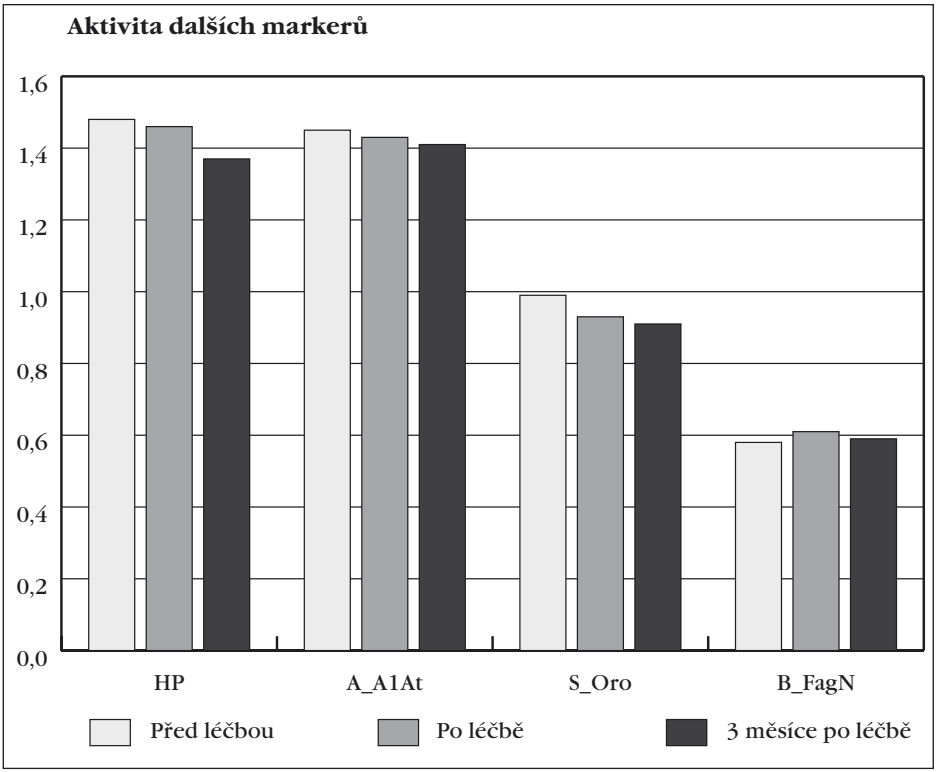
## SEZNAM POUŽITÝCH ZKRATEK

A-1AT – alfa-1-antitrypsin
Bq – Bequeler (SI jednotka radioaktivity)
CRP-C – reaktivní protein
EOAR – ekvivalentní objemová aktivita radonu
FAG – fagocytární aktivita leukocytů
Gy-Gray – SI jednotka absolvované dávky záření
Hp – haptoglobin
HRQol – Health Related Quality of life
(Hodnocení kvality života podmíněné zdravím)
Kor –kortisol v séru
LLJ – Léčebné lázně Jáchymov
MDA – malondialdehyd




**Obr 5.** Aktivita dalších markerů před a po léčbě

Oro – orosomukoid
PA – pohybový aparát
PLZ – přírodní léčebný zdroj
Rn – radon
SÚJB – Státní úřad jaderné bezpečnosti
Sv – Sievert-SI jednotka dávkového ekvivalentu
biologického účinku záření

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# ENGINEERED NANOFIBERS FOR CELL THERAPY AND NANOMEDICINE

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## ABSTRACT

Nanofibers are increasingly used in tissue engineering for medical applications and in recent years, a lot of effort and resources have been infused into biomedical research to better understand how nanofibers interact with the biological system at both cellular and organ levels, optimize and refine the nanofibers and processing parameters, and incorporate the nanofibers for the intended target applications. The electrospinning technology has played an important role in the last decade as the method of choice to prepare nanofibers as it is a relatively straightforward process, extremely controllable, reproducible, and can produce large amount of continuous fibers. Electrospun nanofibers biomimic the structural scaffolds of the interstitial space for cells to organize and assemble into tissues and organs. In this article, we present our research on using electrospinning technology to prepare nanofibers and scaffolds with hierarchical structures which mimic the biological system to address the following biomedical applications: bone regeneration, vascular graft, peripheral nerve repair, skin graft, hepatocyte culture, and nanomedicine.

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## INTRODUCTION

For many years, ceramics, metals, and synthetic polymers have been used as substitutes in healthcare industries to restore functions of defunct tissues and organs. Unlike natural tissues, these materials are non-living and have limited capabilities in restoring full functions. In the past 2 decades, bioengineers have advanced the development of tissue engineered materials in attempt to alleviate the problems of tissue and organ shortage in transplantation. These developments have resulted in biomaterials with biophysicochemical properties intrinsic to the target applications, scaffolds with micro- and nano- structured properties, self-assembling biopolymers, and fibers and scaffolds with biomimetic properties. Approaches employed by bioengineers to restore biological functions include spraying cells onto the target site, printing cells on scaffolds for implants, and seeding cells on porous scaffolds and creating a conducive environment for cells to attach, proliferate, organize, and develop into viable tissue and organ analog before transplantation. The last approach of seeding cells on scaffolds to develop tissues and organs has met with more success in recent times. Advancement in the processing technology of biomaterials and scaffolds, and chemical synthesis of new polymers have played a significant role in the dramatic development of tissue engineering.

With a better understanding of the physicochemical properties of polymers and new chemical synthesis and purification methodologies, polymers are currently widely used in tissue engineering to produce replacement tissues and organs. Polymers can generally be grouped as biodegradable or inert, and comprise both synthetic and natural polymers. To better mimic the micro- and nano- structural fibers of the interstitial space or commonly known as the extracellular matrix (ECM), bioengineers have used various approaches to fabricate scaffolds with fibers in micro- and nano- scale. These include phase separation, self-assembly, mechanical methods, and electrospinning. By far, electrospinning is the most promising technique in producing fibers of nanoscale, the nanofibers which closely mimic the physical structure of the ECM. Being a relatively straightforward process, electrospinning can produce large amount of nanofibers with reproducible and controllable fiber composition, morphology and assembly. To biomimic the natural ECM, nanofiber scaffolds can be fabricated in a hierarchical manner and together with surface and intrinsic modifications by physical and chemical means which can be performed relatively easily on the nanofibers, these will encourage the development of cells into tissues and organs. This in part is largely influenced by the chemical, morphological and mechanical nuances of nanofibers (**1**).

## POLYMERS IN MEDICINE

Natural biomaterials such as collagen, gelatin, chitosan, alginate, and acellular tissue matrices such as small intestinal mucosa have been widely used for cell-based tissue engineering as they have the advantage of biological recognition, and provide a better environment for tissue regeneration. Due to their intrinsic antigenic properties, natural biomaterials may elicit inflammatory and immunological responses. In addition, large scale production and batch variation

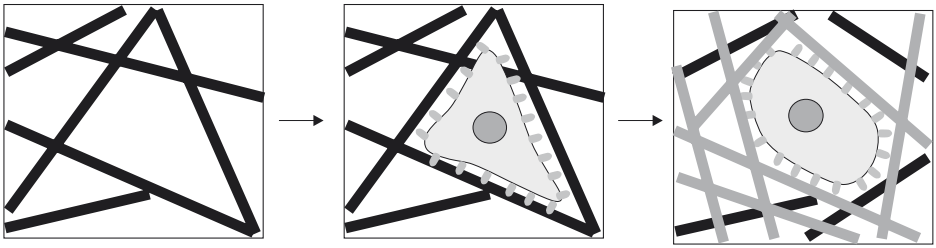

**Figure 1.** Biodegradable synthetic polymer fibers (black) provide more avenues for new tissue regeneration and remodeling with the deposition of natural fibers (grey).

during isolation are some of the other factors limiting full exploitation of natural biomaterials in general for cell tissue engineering and biomedical applications. Synthetic polymers offer greater potentials for biomedical applications as they are more readily available and reliably produced with predictable batch-to-batch uniformity. In addition to being less immunogenic and inflammatory in nature, synthetic polymers can be relatively easily fabricated into numerous compositions, morphologies, and assemblies in a more controlled manner than natural biomaterials.

Both inert and biodegradable synthetic polymers have gained wide applications in medical settings in recent times (**Table 1**). Inert polymers are usually used for permanent or temporary fixtures which require structural and mechanical

| Synthetic Polymers | Biomedical Applications |
|---|---|
| Polyacrylonitrile | Dialysis membranes |
| Polyamides | Dialysis membranes |
| Polydimethylsiloxane | Breast, penile implants |
| Polyethylene | Hip prostheses |
| Poly (ethylene-covinyl acetate) | Drug delivery |
| Poly (2-hydroxyethylmethacrylate) | Contact lenses |
| Poly (l-lactic acid), poly (glycolic acid) | Drug delivery |
| Poly (methyl methacrylate) | Fracture fixation devices, dentures |
| Polypropylene | Plasmapheresis membranes, sutures |
| Polystyrene | Tissue culture |
| Polysulfone | Heart valves, penile implants |
| Poly (tetrafluoroethane) | Heart valves |
| Polyurethanes | Artificial hearts |
| Poly (vinyl chloride) | Plasmapheresis membranes, blood bag |
| Poly (vinyl pyrrolidone) | Blood substitutes |

**Table 1.** A summary of biomedical devices synthesized from synthetic polymers.

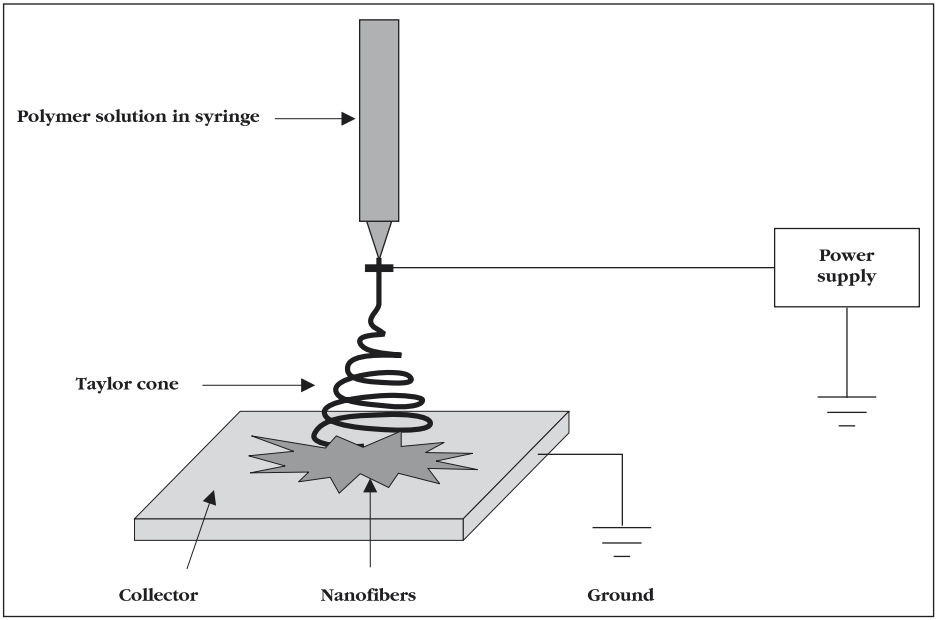


**Figure 2.** Schematic diagram of the electrospinning process.

strength. Examples include polyurethane which is used for artificial heart and heart valves as polyurethane provides the flexibility and fatigue-resistance demanded by the constant motion and friction of the heart and valves (**2**). Synthetic polymers that are biodegradable have more prospect than inert polymers in tissue engineering and biomedical applications, in particular scaffold development for tissue engineering, as implants, and as vector for delivery of drugs and biomolecules to the site of action. Development of scaffolds for tissue engineering and as medical implants have benefited tremendously from the recent advancement in the chemistry, synthesis and understanding of biodegradable synthetic polymers. Scaffolds fabricated from biodegradable synthetic polymers can initially act as support and void tissue fillers for cells to attach, proliferate, and eventual tissue and organ formation to replace or restore loss tissues and organs. Overtime, the biodegradable scaffold undergoes resorption but at the same time, natural ECM are secreted by the adherent cells and tissues to replace the scaffold. This remodeling of the tissue space is a dynamic event involving cell, scaffold, and natural ECM deposition and resorption (**Figure 1**).

Even though biodegradable synthetic polymers may appear as ideal biomaterials to overcome some of the limitations associated with natural biomaterials, the use of biodegradable synthetic polymers are not with any inherent risks. Minimally, these polymers have to be biocompatible with the biological system and the degraded polymers should be either easily metabolized or excreted from the biological

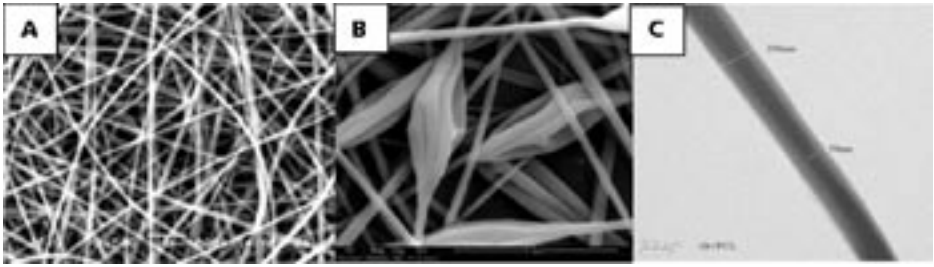


**Figure 3**. Different types of nanofiber morphologies. (**A**) Smooth polysulfone fibers, (**B**) beaded polysulfone fibers, and (**C**) core-shell structure (polycaprolactone shell/gelatin core).

system. These degraded polymers preferably should not elicit local inflammatory response at the site of administration, and should not initiate adverse reaction in the body such as fever. The choice of polymers for a particular application may be different from another scenario, and the localized reaction may be essentially different. Hence, selection of polymers for tissue engineering and medical implants has to be stringent to avoid any adverse reactions.

## ELECTROSPINNING OF NANOFIBERS

One of the most common methods in nanofibers fabrication is the electrospinning method. It involves the use of an electric field to draw a positively charged polymer solution from the needle tip to a ground collector. The solution droplet at the needle tip will distort into a Taylor cone when the electric field is generated by surface charge. Once the electric potential at the surface charge exceeds a critical value, the surface tension of the polymer solution will be overcome by electrostatic forces, resulting in a thin jet of solution erupting from the surface of the cone. While the solvent evaporation takes place, a continuous fiber is collected on an electrically grounded collector (**Figure 2**).

There are three main factors that would influence the electrospinning process. Firstly, they are the polymer solution properties such as surface tension, conductivity, and viscosity, secondly, the controllable variables such as electrical potential and hydrostatic pressure, and thirdly, the ambient parameters such as humidity in the electrospinning chamber, and the type of gas supplied to the chamber in which the nanofibers are electrospun, will influence the electrospinning process as well as the nanofiber characteristics (**3**).

Currently, with the electrospinning process, it is possible to fabricate nanofibers with diameters as thin as 3 nm (**4**). In addition, nanofibers with many different morphologies (**Figure 3**) and assemblies (**Figure 4**) can be easily achieved with different electrospinning setups.

Fabrication of nanofibers by electrospinning offers many advantages; it is able to produce long continuous fibers with a uniform diameter, cost effective and there is a wide variety of polymers that can be electrospun into nanofibers. Polymers that can be electrospun include natural as well as synthetic polymers, such examples are polyurethane, polylactic acid, polystyrene, polymethacrylate, poly(lactide-co-gly-

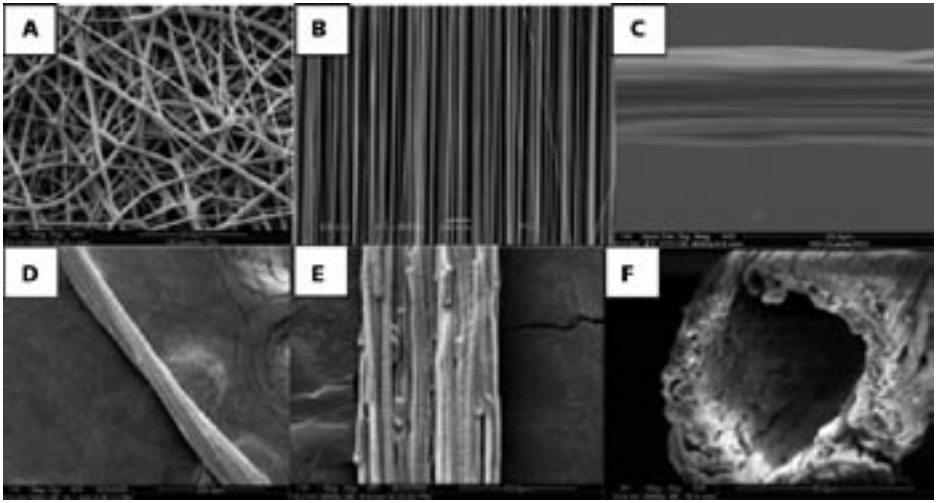


**Figure 4.** Different nanofiber assemblies. (**A**) Random polycaprolactone (PCL) fibers, (**B**) aligned PCL fibers, (**C**) PCL fiber bundles, (**D**) twisted PCL yarn, (**E**) PCL yarn, and (**F**) PCL yarn cross-section.

colide), collagen and polycaprolactone. In addition, by blending polymers together or incorporating additives in the solution, it would allow the electrospun nanofibers to achieve unique fiber compositions (**Figure 5**). With these benefits, electrospinning can serve as a good method for future nanofiber mass production.

## BIOMEDICAL APPLICATIONS OF NANOFIBERS

The advantages offered by the electrospinning technology and the intrinsic favorable properties of nanofibers and biodegradable synthetic polymers can be combined to effectively fabricate scaffolds for tissue engineering and medical implants. The nanoscale topography of the scaffold is particularly important for cell tissue engineering and elucidating the mechanisms of interaction is critical to the success of electrospun biodegradable synthetic polymer nanofibers as biomaterials for tissue regeneration and medical implants. For tissue and organ formation, the cells will first have to attach to the scaffolds, proliferate, organize and remodel the interstitial space, and these are influenced by the mechanical, physical, chemical and biomimetic properties of the scaffolds. Here, we present our research findings and some recent reports on the effects of nanofiber scaffolds and their modifications on cell interaction, and tissue and organ regeneration in the areas of bone regeneration, vascular graft, peripheral nerve repair, skin graft, hepatocyte culture, and nanomedicine.

### Bone Regeneration

Currently, biodegradable polymers are commonly combined with nano-bioceramics either before or after electrospin-

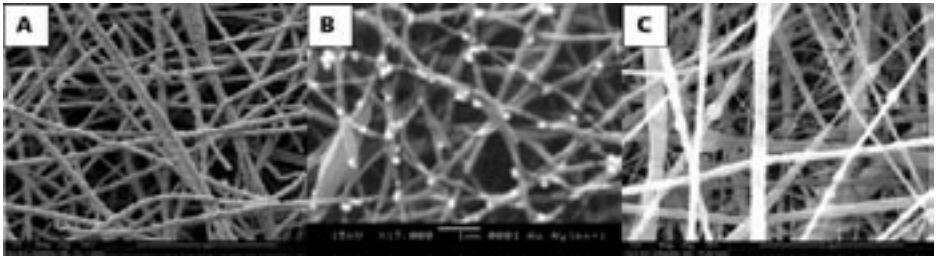


**Figure 5**. Electrospun nanofibers with different fiber compositions. (**A**) Alumina fibers, (**B**) nylon-6 fibers with gold nanoparticles and (**C**) PCL hydroxyapatite nanofibers.

ning process for bone tissue regeneration. Fujihara *et al.,* (**5**) prepared the PCL/$CaCO_3$ composite electrospun fibers to encourage the osteoblasts attachment from the *in vitro* experiments. Alternatively, the electrospun nanofiber film was soaked in simulated body fluid (SBF), as seen in the study of Ito et al., (**6**). However, hydroxyapatite (HA) composition did not significantly affect the cell adhesion on mineralized silk/polyethylene oxide (PEO) electrospun nanofibers containing poly(L-aspartate) (poly-Asp) (**7**). It is highly possible to develop mineralized nanofibers, but it is also necessary to investigate the cellular behavior for instance osteoblasts or other cell types on mineralized nanofibers for a more representative analysis.

Mesenchymal stem cells (MSCs) that are derived from the bone marrow of neonatal rats were seeded on electrospun PCL scaffolds by Yoshimoto et al., (**8**). The cell-polymer constructs were cultured with osteogenic supplements under dynamic culture conditions. At 4 weeks, the surfaces of the cell-polymer constructs were covered with multi-cellular layers. In addition, both type I collagen secretion and cell mineralization could be detected. Gelatin/PCL composite electrospun nanofibers were fabricated by mixing the solutions of 50% gelatin solution and 50% PCL solution (**9**). Contact-angle measurement and tensile tests indicated that the gelatin/PCL complex fibrous membrane exhibited improved mechanical properties as well as a more favorable wettability compared to those of pure gelatin or PCL nanofibers. MSCs could not only favorably attach and grow well on the surfaces of these scaffolds, but were also able to migrate into the scaffold up to 114 μm within 1 week of culture. These results imply that there is better biocompatibility in gelatin/PCL composite electrospun nanofibers than pure PCL nanofiber material. Such promising observations of MSC on nanofibers matrix can be seen on PLA and silk electrospun nanofibers (**10, 11**).

One the other hand, bone growth factors such as BMP-2 and OP-1 gradually became attractive clinical drugs for bone defects repair. Fortunately, the mild aqueous process required to electrospin the fibers offers an important option for delivery of labile cytokines and other biomolecules into the system. In principle, the absorption of growth factors is more predominant on nanofiber materials due to its high surface area as compared to conventional materials. In essence, nanofibers are deemed to give rise to a more optimal healing effect. The silk fibroin nanofiber scaffolds containing BMP-2 and/or nanoparticles of hydroxyapatite (nHA) prepa-

red via electrospinning were selected as a matrix for *in-vitro* bone formation from human bone marrow-derived mesenchymal stem cells (hMSCs) (**12**). The scaffolds with the co-processed BMP-2 supported higher calcium deposition, higher crystallinity apatite and enhanced transcript levels of bone-specific markers than in the controls (without BMP-2), indicating that these nanofiber electrospun silk scaffolds were an efficient delivery system for BMP-2. The more important aspect in this study is that the co-existence of BMP-2 and nHA in the electrospun silk fibroin fibers resulted in the highest calcium deposition and up-regulation of BMP-2 transcript levels when compared with the other systems, which makes the nHA/nanofiber composites with BMP propitious for bone graft applications. Electrospun nanofiber/nHA based composites used as scaffold materials for bone tissue engineering will provide an ideal biomimetic environment for osteoblasts in-growth which in turn result in new bone tissue regeneration.

## Vascular Graft

Cardiovascular disease is the leading cause of death in the world. Each year, more than 600,000 coronary and peripheral vascular bypass graft procedures are performed in the United States and Europe, creating an important demand for small diameter (< 6 mm) vascular grafts. Current research in tissue engineered vascular grafts have focused on the use of nanofiber conduits cultured with cells *in vitro* to achieve the desired physical, mechanical and biological properties of natural blood vessels before implantation into the test subjects. Our approach in vascular graft research focused on the development of small diameter vascular grafts that incorporate living smooth muscle cells (SMCs) and fibroblasts embedded in provisional ECM composed of biodegradable polymers and biological proteins, which would ultimately be lined with endothelial cells (ECs) to provide a living, responsive, non-thrombogenic blood conduit that is mechanically reliable and immunologically safe.

In the blood vessels, the SMCs are arranged circumferentially, the ECs are arranged along the direction of blood flow, while the fibroblasts are randomly arranged occupying the outer most layer of the blood vessels. We have shown that SMCs cultured on aligned nanofiber P(LLA-CL) (75:25) scaffold (**Figure 6a**) showed a favorable interaction between the cells and the scaffold: the SMCs attached and migrated along the axis of the aligned nanofibers and expressed a spindle-like contractile phenotype; the distribution and organization of smooth muscle cytoskeleton proteins inside SMCs were parallel to the direction of the nanofibers (**Figure 6b**); the adhesion and proliferation rate of SMCs on the aligned nanofiber scaffold was significantly improved than on the plane P(LLA-CL) film (**13**). In addition, we have demonstrated that ECs proliferated well on protein-modified scaffolds, in this particular case collagen-blended P(LLA-CL) nanofibrous scaffolds (**Figure 7**), but not on unmodified scaffolds (**14**), which is critical for the endothelialization of the vascular graft to prevent thrombosis. Hence, by using random, aligned, and core-shell structured nanofibers, we can construct a conduit with different fiber orientation to direct cell growth, and encapsulating biomolecules to enhance cell proliferation.

To ensure that the cell-based vascular graft attain sufficient mechanical proper-

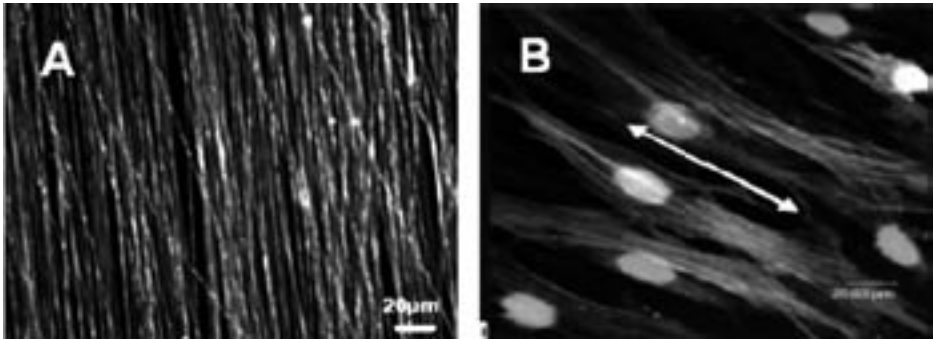


**Figure 6**. Optical micrographs of aligned P(LLA-CL) nanofibrous scaffold fabricated by electrospinning (**A**), and expression of immunostained α-actin filaments in SMCs after 1 day of culture on aligned nanofibrous scaffold (**B**). (Reproduced from (**13**) with permission, copyright 2004 Elsevier).

ties equivalent to that of the blood vessels, a bioreactor was designed and developed for this study (manuscript in preparation). This *in vitro* cell culture system can provide adjustable pulsatile forces and shear stress forces by the flow of nutrient medium through the developing vascular graft to mimic the *in vivo* hemodynamic conditions. The mechanical stimuli under dynamical culture would biomechanically remodel the vascular cells and increase the grafts patency rate. Using this system of nanofiber scaffold with predetermined fiber orientation and the bioreactor, we have been able to develop a cell-based nanofiber vascular conduit (**Figure 8**) but this research is very preliminary and there is much to be investigated. Acellular vascular conduits were also fabricated to evaluate thrombogenicity of P(LLA-CL) nanofi-

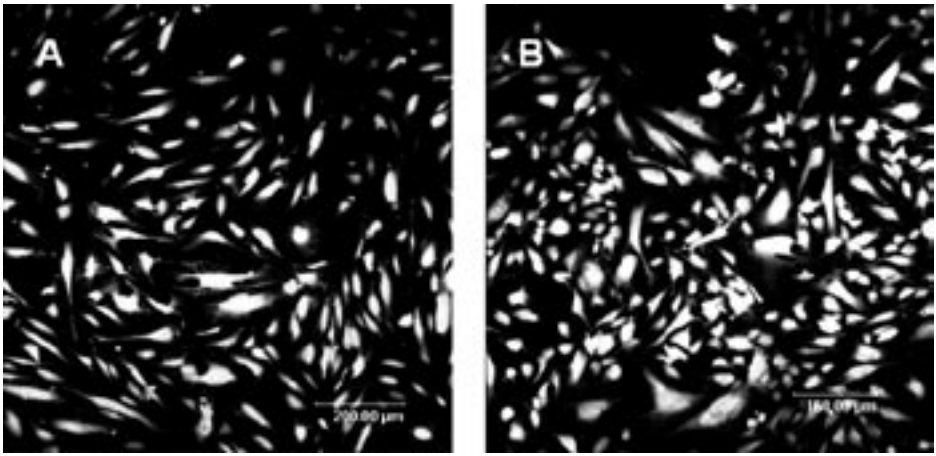


**Figure 7**. ECs cultured on tissue culture polystyrene surface (**A**) and collagen-blended P(LLA-CL) (**B**) nanofibers.

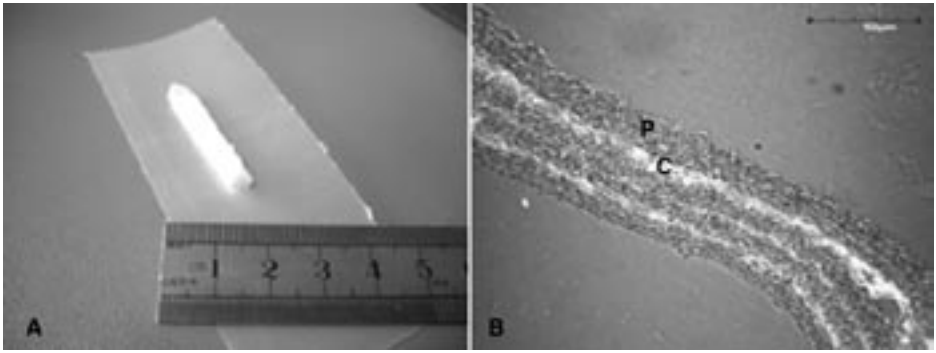


**Figure 8**. Photograph of tissue engineered vascular graft model (**A**), and immunofluorescence staining of α-actin (**B**) where P: polymer and C: positive staining of SMCs.

ber surface. The conduits were implanted in a rabbit epigastric vein transplantation model for 7 weeks. Hematoxylin and eosin staining of the explanted graft did not reveal any thrombogenesis (manuscript in preparation). Hence, the nanotopography and orientation of the fibers, and the use of a dynamic bioreactor may contribute to the success of a cell-based tissue engineered vascular graft.

## Peripheral Nerve Repair

Peripheral nerve tissue engineering is another field that can utilize the versatility of electrospinning technique to fabricate

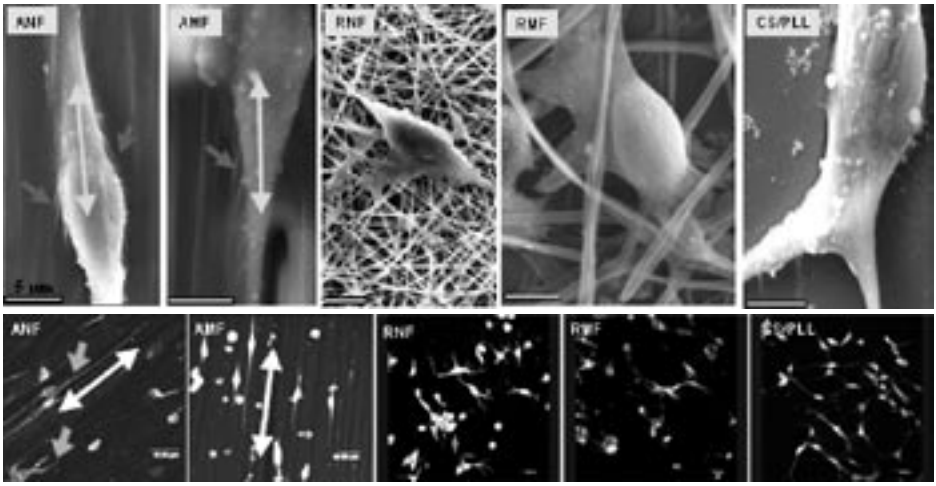


**Figure 9**. (a) Phase contrast micrographs (b) Confocal laser scanning micrographs (staining of neurofilament 200 kDa): neural C17.2 cells interactions with nanofibers on day 2 after cell seeding: ANF, AMF, RNF, RMF – aligned and random nano- or micro- fibrous scaffolds; CS/PLL – poly L-lysine coated solvent cast film. (Reproduced from (16) with permission, copyright 2005 Elsevier).

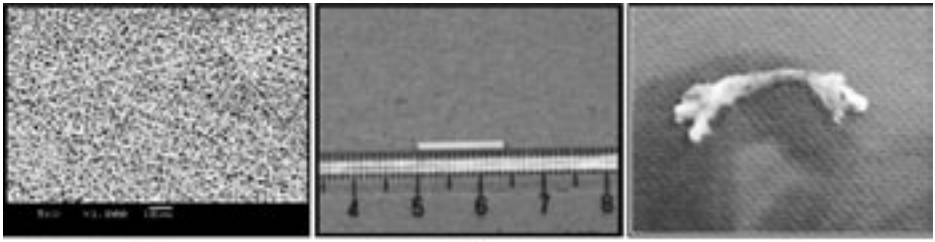


**Figure 10**. (a) Scanning electron micrograph of electrospun PLGA conduit surface (b) Marcograph of PLGA conduit (c) Explanted nerve regenerated nerve cable after one month of implantation. (Reproduced from (**17**) with permission, copyright 2004 Institute of Physics Publishing).

scaffolds or nerve guidance channels with different arrangements or morphologies (**15**). Study has been shown that neural stem cells, C17.2, could adhere and proliferate well on electrospun scaffolds and the differentiation rate of the cells were observed to be better on nanofibrous scale compared to that of the microfibrous scale (**Figure 9a**) (**16**). In addition, the fiber arrangement might have effects on the mediation of the interaction of the neural cells with the scaffolds such that the neurite outgrowth of the cells was parallel along the alignment of the electrospun fibers (**Figure 9b**) (**16**). Analysis has also shown that through contact guidance effect, the aligned nanofibrous scaffolds were able induce more than 90% of cells to elongate neurite parallel to the fiber axis and to promote the longest neurite extension as compared to the other materials studied (**16**).

Nerve guidance channels for peripheral nerve tissue engineering can be efficiently fabricated by the electrospinning method. Bini *et al.* fabricated poly (L-lactide-co-glycolide) (PLGA) biodegradable polymer nanofiber conduits via the electrospinning technique (**Figure 10a and 10b**). The study demonstrated that the artificial nerve conduits were flexible, permeable. *In vivo* study showed that none of the implanted tubes showed breakages and the tubes did not elicit inflammatory response in the rat sciatic nerve model after one month of implantation (**17**).

Comprehensive analysis of the immunological staining for neurofilament protein, NF68, and histological studies (**Figures 11 and 12**) illustrate that electrospun nanofibrous nerve guidance channels could support nerve regeneration. Both myelinated and unmyelinated axons were observed in the explanted nerve cable (**Figures 10c and 12**) that was repaired with the assistance of the nanofiber conduits (**17**). Therefore, electrospinning would be one of the most interesting methods to fabricate artificial nerve conduits possessing good capacity to enhance axonal regeneration.

## Skin Graft

Skin loss can result from burns, trauma, chronic wounds, and skin tumors. Autologous, allogenous, and xenogenous skin grafts, and artificial wound dressings may not completely satisfy clinical demands for severe burn and chronic wound patients as there is a limit to the area of normal skin for grafting, and possible immunore-

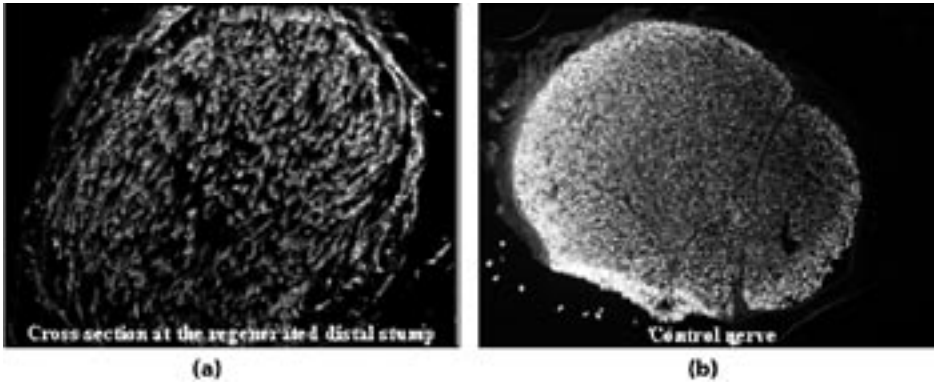


**Figure 11**. Immunostaining for the neurofilament protein (NF68) confirmed axonal distribution of the regenerated nerves in the nanofiber conduits. Cross-sectional view of the (a) conduit regenerated distal stump (b) control rat sciatic nerve. (Reproduced from (**17**) with permission, copyright 2004 Institute of Physics Publishing).

jection. Tissue engineered skin construct which includes a scaffold, support cells, growth factors, and extracellular matrix is an alternative skin engraftment to facilitate wound healing. In addition to epidermal cells, bone marrow-derived stem cells can also be used to stimulate effective skin regeneration in acute cutaneous wounds, chronic non-healing wounds and deep burn wounds.

Both naturally derived and synthetic polymers have been developed as scaffolds for culturing human fibroblasts and keratinocytes. Among the naturally derived

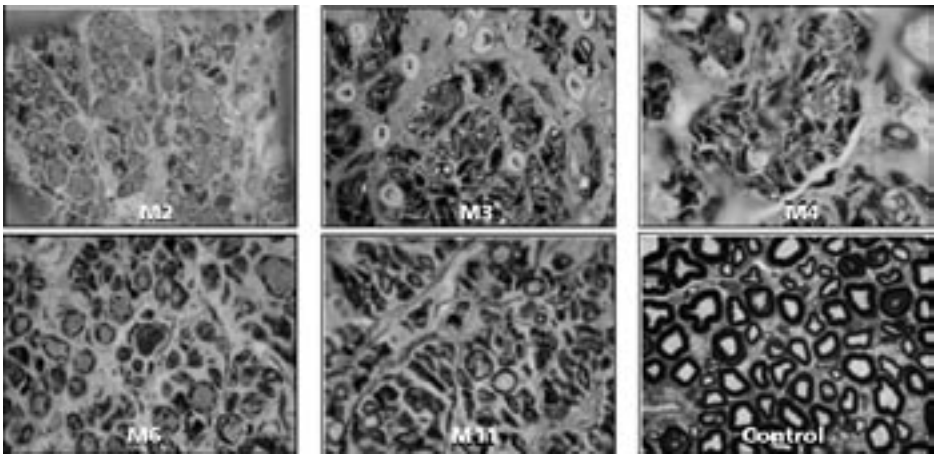


**Figure 12**. Histology analysis of the varying degrees of myelinated axons in regenerated rat sciatic nerves in the nanofiber conduits. (Reproduced from (**17**) with permission, copyright 2004 Institute of Physics Publishing).

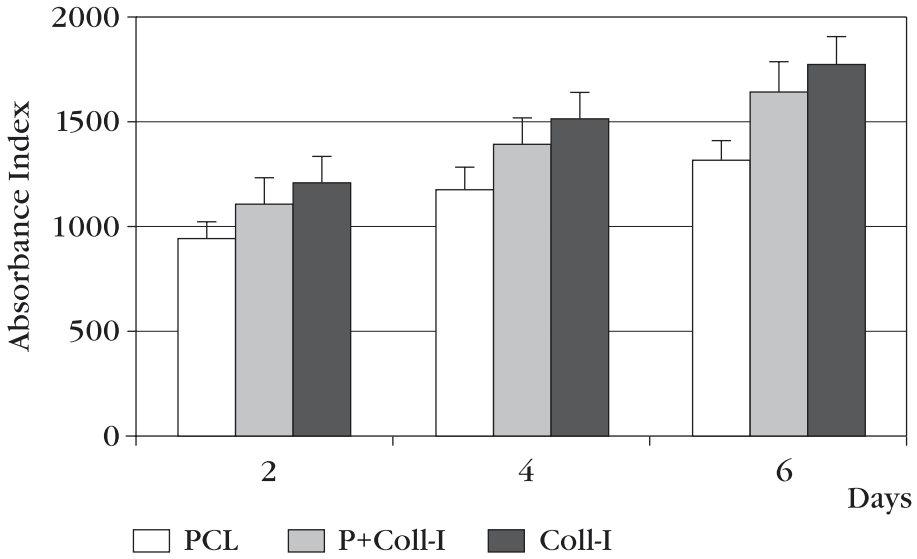


**Figure 13**. PCL-collagen type-I blended nanofiber scaffold enhanced human dermal fibroblast proliferation.

polymers, collagen scaffolds alone or in combination with other ECM components such as glycosaminoglycan (GAG) and growth factors to improve cell attachment and proliferation, have been widely used for skin tissue engineering. Despite the advantages of naturally derived polymers such as biological recognition and provide a better environment for tissue regeneration, the scaffolds lack mechanical strength and are rapid absorbed. To overcome these limitations, synthetic biodegradable polymers have been used as scaffolds for skin regeneration. Examples include poly(lactic acid) (PLA), poly(glycolic acid) (PGA), poly(DL-lactic-co-glycolic acid) (PLGA), and poly(ε-caprolactone) (PCL). However, synthetic polymers are normally more hydrophobic compared to natural polymers, and generally lack biological recognition. Hence they may not readily promote skin regeneration.

In our research, we complement the beneficial properties of naturally-derived polymers and synthetic polymers to electrospin nanofiber scaffolds that not only possessed nanotopography but also biological recognition and mechanical strength for cells to attach, proliferate and skin regeneration. Using PCL and collagen type-I, we prepared a blended nanofiber scaffold which readily enhanced human dermal fibroblast attachment and proliferation as determined by cell proliferation assay (**Figure 13**). This PCL-collagen type-I blended nanofiber scaffold can be used as autologous or allogenous cultured dermal substitute in patients with extreme burns and chronic wounds (**Figure 14**). In addition to dermal fibroblasts, bone

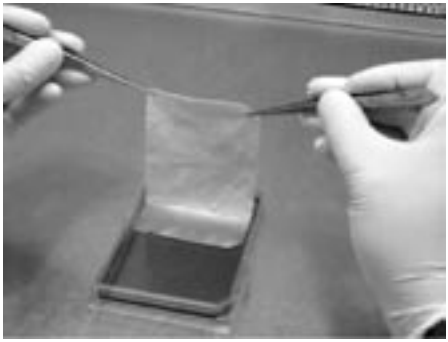

**Figure 14**. Autologous/allogenous cultured dermal substitute composed of dermal fibroblasts and PCL-collagen type-I blended nanofiber scaffold.

marrow-derived stem cells can also be seeded on PCL-collagen type-I blended nanofiber scaffold and applied to the wound to enhance skin regeneration. Currently, we are investigating this approach in skin regeneration and we have demonstrated that PCL-collagen type-I blended nanofiber scaffold provide a good substrate for bone marrow derived stem cells to attach (manuscript in preparation). The results are very preliminary and there is much to be understood in stem cell interaction with the nanofiber scaffolds.

## Hepatocyte Culture

Nanofiber scaffolds modified with surface-galactose ligand (Gal-mesh) can be used as a template for hepatocyte attachment in liver tissue engineering. Galactosylation greatly enhances the adhesion efficiency as the galactose-asialoglycoprotein receptor (ASGPR) mediates hepatocyte adhesion. Most of the hepatocyte functions are also retained as the surface modification minimizes the integrin-mediated pathway which is known to result in the loss of hepatocyte phenotype.

Besides ligand-receptor interactions, substrate topology also influences hepatocyte behavior and morphology. Reported by Chua *et al*., (**18**) hepatocyte spheroids formation on Gal-mesh was small and fairly uniform (20–100 μm in diameter) while spheroid formation on Gal-film was larger with a wider distribution (50–300 μm in diameter). In addition, Gal-mesh spheroids engulfed functional nanofibers and had a flattened morphology (**Figure 15d-f**) while Gal-film spheroids did not integrate with the substrate and were rounded in appearance (**Figure 15a-c**). As a result, cell attachment was stronger for Gal-mesh than Gal-film. The high cell immobilization efficiency of the Gal-mesh helps hepatocytes to maintain their differentiated functions and remain stable against perfusion and shear forces in bioreactors, hence making it suitable for use in bioartificial liver-assist devices.

Functional profiles like percentage cell attachment, ammonia metabolism, albumin secretion and cytochrome P450 enzymatic activity seem to be independent of substrate topology. It appears that as long as individual hepatocytes are held by cell-cell contacts in a spheroid (regardless of flat or round), viability and functions would be maintained. However, due to the overall complexity of hepatocyte functional maintenance, a combination of biochemical and topological cues from the nanofiber scaffold may influence cultured hepatocyte functions to varying extents. This remains to be investigated.

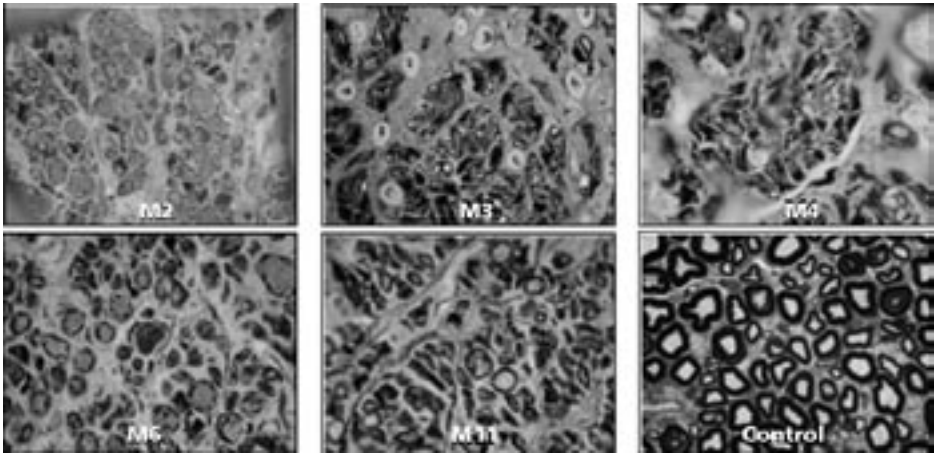


**Figure 15**. SEM images of hepatocytes after 8 days of culture: (a–c) hepatocytes cultured on Gal-film formed rounded spheroids that did not integrate with the scaffold; (d–f) in contrast, hepatocytes cultured on Gal-mesh showed that the aggregates engulfed the functional nanofibers. (Reproduced from (**18**) with permission, copyright 2005 Elsevier).

# NANOMEDICINE

## Drug/Gene Delivery

In order to deliver the minimum required amount of drugs to the diseased/trauma site, drug delivery systems have been developed using polymeric materials in the form of nano or micro particles, hydrogels and micelles. Although these materials improve the therapeutic effects and reduce side effects, there is still a need to address the issue of precise control of the rate of drug release. Thus, researchers have recently focused on the usage of polymer nanofibers to encapsulate medical drugs. Drug chemical component is mixed in the polymer solution and nanofibers are electrospun with the drug. Polymeric materials included PLLA, PU, HPMA, PLA/PEA, PLGA and PLGA/PEG-PLA are already used as carriers for many antibiotics, anti-cancer and anti-tuberculosis drugs, and for the treatment for Tinea Pedis, wound healing, periodontal disease etc. There is an optimum range of the drug release per unit time after the patient consumes the medicine. Herein, we need to avoid the initial burst of drug release as seen in conventional delivery systems. But depending on the type of medical treatment, burst drug release is preferred in those administering antibiotics. Electrospinning of nanofibers will render various types of nanofibers with controllable component and size to meet different requirements of the applications. For example, the distribution of fiber diameter has to be minimized for burst drug release. The core-shell structure of bi-component nanofibers and porous nanofibers developed by Zhang *et al*., (**19, 20**) provides more options for short term and long term release. In this case, we incorporated different drugs into the

bi-component system to achieve a more effective medical treatment.

Gene therapy is at the forefront of medical technology which focused on correcting the defective genes that are responsible for a disease. These novel drugs have been designed to act against specific targets or receptors in the body. Although they have proved effective in the laboratory settings, the success in clinical studies is limited. The paramount reason is that there is no effective carrier for these drugs to reach to their intended targets. Nanofibers developed by electrospinning seemed to be highly viable for gene therapy, because design and material parameters such as nanopores and nanoparticles be manipulated and incorporated into the nanofibers during electrospinning process. However, drug delivery in the form of nanofibers is still in the early stage of exploration, and the real delivery mode and its efficiency are yet to be determined.

### Nanodevices

Nanofibers can also be fabricated from shape-memory materials (**21**). These materials can be implanted into the body using a laparoscope (a long, slender medical instrument for examining the interior of an organ or to perform minor surgery), minimizing complex surgical procedures. The fibers then change shape in response to the increase in temperature. Because of the large surface-to volume ratio, nanofibers can also be used in diagnostics for large-scale disease and genetic screening. Conductive nanofibers are expected to be used in the fabrication of tiny electronic devices or machines such as sensors. To fully mimic organ functions, for example, secretagogue-triggered hormone release, miniaturization of sensors to nanodimensions may decrease the typical time constant down to the milliseconds time scale (**22**), which is very close to the trigger system in a normal human body. Owing to ultra small size of nanofibers which offer capacious advantages, nanosensors can be easily embedded into the scaffold, even in cell membranes to establish smart/responsible implantable tissue grafts. Arrays of conductive nanofibers coated with different anti-bodies or nucleic acids can be used to detect thousands of genes in a cell and proteins synthesized by a cell. For instance, the nanofibers can be specially bound to a protein expressed by cancer cells. For the diagnostic and treatment for the patients, nanofibrous devices can be broadly used for medicine. Moreover, if we combine the antibody for diagnostic and drugs for therapy into a single nanofiber and induced the trigger for local release on nanoresolution into it, we will realize the precise nanotherapy for the maximum benefits to patients.

## FUTURE OUTLOOK

In retrospect of the nano world in nature, nanofibers exist similarly to different patterns as extracellular matrix (ECM). Alternatively, the advanced electrospinning nanotechnology is an available way to fabricate controllable continuous nanofiber scaffolds similar to the ECM. This biomimetic aspect as a distinct foundation, will definitely promote the development of nanomedicine with development of nanofibers. However, most current nanofiber research is still at the experimental stage. The trend is heading to animal studies and clinical trials, aimed to achieve the biomedical applications. The use of nanofibers

as a hopeful therapy including stem cells implantation will provide a springboard for us to spearhead areas in cell therapy and nanomedicine. In conclusion, nanofibers as powerful and novel tools will accelerate the development of nanomedicine, which will be the new medicine of the 21st century as customized treatments and therapies will target specific diseases and disorders and eradicate pain and suffering in the patients.

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# ETICKÁ PROBLEMATIKA GENETICKÉHO PORADENSTVÍ

# ETHICAL PROBLEMS OF GENETIC COUNSELLING

**KUČEROVÁ M.**

Ústav biologie a genetiky, 3. LF UK Praha

## SOUHRN

**Genetické poradenství** se dotýká mnoha etických problémů a je nutné,aby kliničtí genetici toto respektovali a přistupovali ke své práci z tohoto hlediska.Také genetický výzkum, který se velmi rychle a nadějně vyvíjí se musí řídit velmi přísně etickými pravidly.

**Klíčová slova:** lékařská etika, genetické poradenství, etická pravidla genetického výzkumu.

## SUMMARY

**Genetic counselling** includes many ethical problems and it is necessary to include this view by clinical geneticists during their work.Also genetic research ,which is developing very quickly and brings many hopes must be doně under strict ethical rules.

**Key words:** medical ethics, genetic counselling,ethical rule sof genetic research

V genetickém poradenství je nutné se řídit základními zásadami etiky, mezi které patří:

- neautoritativní přístup
- empatie – odhad reakce postižených a vhodný psychologický přístup
- pravdivé a srozumitelné seznámení pacienta a členů rodiny se všemi skutečnostmi a možnostmi prevence a eventuelní léčby, nebo zlepšení onemocnění
- zachovávání lékařského tajemství
- další potenciálně ohrožené členy rodiny je možné informovat jen se souhlasem postiženého
- je vhodné uchovávání vzorků DNA postižených pro eventuelní možnost budoucího vyšetření stejně tak i lékařskou evidenci postižených rodin pro možné využití v dalších generacích.

Velmi citlivá je oblast genetického poradenství v oblasti prenatální diagnostiky. Je třeba respektovat přístup k řešení situací rodin, u kterých byl diagnostikován během těhotenství patologický plod. Otázku ukončení gravidity musí rozhodnout samy rodiny, nikoli lékař-genetik. Na příklad při zjištění plodu s abnormalitou pohlavních chromosomů se téměř polovina rodin rozhoduje si plod ponechati informace o patologických hodnotách biochemického screeningu v graviditě musí zahrnovat vysvětlení existence malého procenta falešně pozitivních i negativních výsledků, které upřesní až prenatální diagnostika.

V oblasti molekulární genetiky je problematická situace, kdy i pro častější genetická onemocnění existuje široká škála a množství mutací a možnost testovat jen ty nejčastější. I to je nutné postižené rodině srozumitelně vysvětlit.

Komplikovaná je i problematika genetického testování dětí a adolescentů, kteří nemají klinické obtíže, ale jsou potenciální nosiči patologických genů (heterozygoti autosomálně recesivních genů, recesivních chorob vázaných na pohlaví) nebo balancovaných chromosomálních aberací, nebo markerů. Toto testování se provádí pouze z hlediska možného genetického postižení potomstva těchto jedinců. Mezinárodní diskuse o tomto problému a její závěry doporučují testovat a informovat o výsledcích jedince až od věku 18 let a výše. Až v tomto věku jsou jedinci schopni pochopit a zhodnotit výsledky genetického testování.

Jsou stanovena i mezinárodní pravidla pro netherapeutické mezinárodní studie, které často probíhají v rozvojových zemích. Všichni účastníci výzkumu musí s ním souhlasit a jejich účast musí být finančně kompenzována. Materiály musí být anonymní a měly by být k dispozici i pro budoucí výzkum. Účastníci by měli být informováni o výsledcích studie. Diskutuje se též, zda politici mohou ovlivňovat podporu nebo odpor proti teoretickému výzkumu. Příkladem jsou obtíže amerických vědců při molekulárním výzkumu embryonálních buněk, které jsou velkou nadějí pro možnosti řady genetických chorob v budoucnosti.

UNESCO již v roce 1999 vydalo univerzální deklaraci o lidských právech a lidském geonomu. Tato deklarace doporučuje, aby výzkum a diagnostika lidského geonomu byly prováděny jen po pečlivém zvážení všech možných rizik a pozitivních účinků. Je vyžadován informovaný souhlas všech osob, kterých se to týká. Nikdo nesmí být diskriminován na základě výsledků genetického testování. (O výsledcích genetických testů zaměstnanců nesmí být informováni zaměstnavatelé – například). Pozitivní a závažné výsledky genetického výzkumu musí být přístupné mezinárodně vědecké a lékařské veřejnosti. Nejen vědci a lékaři jsou vázáni etickými pravidly v informacích o lidském geonomu, ale též veřejná media. Všechny státy by měly podporovat výzkum lidského Geonomu a chránit z tohoto hlediska lidská práva a ohlídat, aby jeho výsledky nebyly využity pro válečné účely. V rámci všech států by tuto oblast měly chránit a uskutečňovat etické výbory a právníci.

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# PLÁNOVANÉ ODBORNÉ AKCE SPOLEČNOSTI PRO POJIVOVÉ TKÁNĚ A ODBORNÉ POLEČNOSTI ORTOPEDICKO-PROTETICKÉ ČLS JEP NA ROK 2007

# SCHEDULED ACTIONS OF THE SOCIETY FOR CONNECTIVE TISSUE AND SOCIETY FOR PROSTHETICS AND ORTHOTICS, CZECH MEDICAL ASSOCIATION OF J. E. PURKYNĚ FOR THE YEAR 2007

**The 8th Prague-Sydney-Lublin Symposium, 20.–21. 4. 2007, Lublin.**
Kontaktní osoba / contact person: **Prof. Tomasz Karski, MD, PhD**
*Chair and Department of Pediatric Orthopedics and Rehabilitation,*
*Medical University of Lublin / Poland*
20-093 Lublin, Chodźki 2 Street, Tel./fax: 0048 81 741 56 53, E-mail: tkarski@dsk.lublin.pl

**Visit of Prof. Kazimierz Kozlovski, 14.–18. 5. 2007, Prague.**
Plánována společná večeře / scheduled dinner (výbor SPT ČLS JEP a RR PÚ) 16. 5. 07
Case presentation conference 17. 5. 07 v Ambulantním centru, Olšanská 7, 130 00 Praha 3.
Kontaktní osoba / contact person: **Doc. MUDr. Ivo Mařík, CSc.**
*Ambulantní centrum pro vady pohybového aparátu*
Olšanská 7, 130 00 Praha 3, Česká republika,
Tel./fax: 222 582 214, E-mail: ambul_centrum@volny.cz

**The 9th Prague-Sydney Symposium and Kubát´s Podiatric day, 19.–20. 10. 2007, Prague**
Kontaktní osoba / contact person: **Doc. MUDr. Ivo Mařík, CSc.**
*Ambulantní centrum pro vady pohybového aparátu*
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# PŘIHLÁŠKA

řádného člena

## Společnosti pro pojivové tkáně ČLS JEP

**Příjmení** ..... **Jméno** .....

**Titul(y)** .....

**Datum narození** ..... **Rodné číslo** .....

**Adresa pracoviště** .....

..... **PSČ** ☐☐☐ ☐☐

**Telefon** ..... **Fax** .....

**Adresa bydliště** .....

..... **PSČ** ☐☐☐ ☐☐

**Telefon** ..... **Mobil** .....

**E-mail** .....

**Přihlašuji se za řádného člena Společnosti pro pojivové tkáně ČLS JEP (odborná společnost 1200) a souhlasím s posláním a cíli České lékařské společnosti J. E. Purkyně.**

**Datum** ..... **Podpis** .....

Stanovisko organizační složky:

**Přijat dne** ..... **Podpis** .....

Přihlášku do společnosti doručte na adresu:

**Společnost pro pojivové tkáně ČLS JEP, Olšanská 7,**
**130 00 Praha 3, ČR, tel./fax: 222 582 214, e-mail: ambul_centrum@volny.cz**

Informace uvedené na tomto formuláři jsou přísně důvěrné a nebudou poskytnuty žádné další osobě ani organizaci.

# INFORMACE O SPOLEČNOSTI PRO POJIVOVÉ TKÁNĚ ČLS J. E. PURKYNĚ (SPT)

Vážená paní kolegyně, vážený pane kolego,

dovolujeme si Vás informovat o možnosti stát se členem **Společnosti pro pojivové tkáně** *(SPT),* která v roce 2004 navázala na plodnou desetiletou činnost Společnosti pro výzkum a využití pojivových tkání vedenou panem prof. MUDr. M. Adamem, DrSc. Posláním *SPT* je podpora rozvoje výzkumu pojivových tkání, šíření nových poznatků týkajících se všestranných analýz tkání z obecného pohledu, moderních klinických přístupů k diagnostice a léčbě. Dalším posláním *SPT* je usnadnění styků mezi jednotlivými odborníky navázáním spolupráce s různými vědeckými, odbornými, výrobními a farmaceutickými společnostmi.
Vědecké poznání a aplikace nejnovějších poznatků v klinické praxi nabyly v posledních letech nebývalého zrychlení, a to nejenom v zahraničí, ale i u nás. Tato skutečnost bezprostředně souvisí s kvalitativním rozvojem poznání i v nebiologických vědách a v moderních inženýrských přístupech. Stále více se prokazuje, že vše se vším souvisí – není náhodou, že nové poznatky a objevy vznikají na rozhraní oborů a různých vědních disciplin. Lidská společnost v posledních desetiletích dosáhla nové civilizační kvality – ve vědě a v jejich aplikacích zcela jistě, avšak v morálce a etice ne tak příliš. Biomedicína je v současné době rozsáhlou interdisciplinární vědou, která bez kooperace s jinými vědními obory by byla odsouzena ke stagnaci. Proto cílem *SPT* je nejenom integrovat odborníky v biomedicíně, ale i v technických sférách.
Prioritní snahou *SPT* je presentovat odborné veřejnosti a specialistům v klinické praxi nejnovější poznatky v oblasti pojivových tkání. *SPT* je i společenskou organizací klinických pracovníků, vědců, pedagogů, která si klade za cíl společensky sblížit nejenom pracovníky v aktivní službě, ale i kolegyně a kolegy v důchodovém věku a v neposlední řadě i studenty a mladé doktorandy z vysokých škol, universit a akademických ústavů.
*SPT* bude organizovat během každého roku alespoň dvě odborná a společenská setkání, kde vedle odborných přínosů bude kladen důraz také na společenské – přátelské diskuse všech vás, kteří nechtějí stagnovat, a kteří nechtějí přemýšlet o nových poznatcích izolovaně a osamoceně.
Pro uhrazení nejzákladnějších nákladů na korespondenci se členy společnosti, jejich informovanost a pořádání odborných kolokvií, symposií a společenských odborných setkání byl stanoven **roční členský příspěvek pro aktivní kolegyně a kolegy 200 Kč** a **pro studenty a důchodce 100 Kč.**
*SPT* vydává časopis *Pohybové ústrojí – pokroky ve výzkumu, diagnostice a terapii,* do kterého se i vy můžete aktivně zapojit odbornými články, vašimi zkušenostmi a slunečnou pohodou. **Předplatné časopisu** zůstává **240 Kč ročně,** pro zahraniční odběratele **12 Euro.**
Milí kolegové, nestůjte (pro katastrofální nedostatek času) opodál a připojte se k české inteligenci – v oblasti pojivových tkání, ke které i Vy zcela jistě patříte. V naší krásné české zemi je třeba, aby prameny poznání byly stále živé a permanentně udržované. Poslání každého z nás není náhodné. Jsme velice zavázáni našim předkům, kteří rozvíjeli kvalitu odbornosti v naší zemi. Nepřipusťme útlum vědy u nás. Nenechme se zmanipulovat programovanou lhostejností, vyrůstající z neodbornosti, závisti a z patologického prosazování ekonomicko-mocenských zájmů.

Těšíme se na Vás a na Vaše zkušenosti – přijďte mezi nás!

**Za výbor společnosti:**
Doc. MUDr. Ivo Mařík, CSc. – předseda
Prof. Ing. Miroslav Petrtýl, DrSc. – místopředseda
Prof. MUDr. Josef Hyánek, DrSc. – místopředseda
Ing. Hana Hulejová – jednatel
As. MUDr. Miloslav Kuklík, CSc. – pokladník

# INFORMATION ABOUT SOCIETY FOR CONNECTIVE TISSUES CMA J. E. PURKYNĚ (SCT)

Dear Sir/Madam, dear Colleagues,

We have great pleasure to inform you about the possibility of joining the **Society for Connective Tissues** (SCT) that was established in 2004 in order to continue the ten-year fruitful activities of the Society for Research and Use of Connective Tissue headed by Professor M. Adam, MD, DSc. The activities of the SCT are aimed at supporting the research development in the field of connective tissues, the dissemination of knowledge related to the all-purpose analyses of the tissues in general, and the application of the up-to-date approaches to the diagnostics and clinical practice. Further, the SCT is determined to facilitate contacts between the respective specialists by means of collaboration with various research, professional, production and pharmaceutical companies.

In the last few years, the scientific knowledge and the application of the latest findings in the clinical practice have accelerated on an unprecedented scale, not only abroad, but also in this country. This fact is closely connected with the qualitative development of the knowledge in the non-biological sciences and in the up-to-date engineering approaches. The fact that all things are mutually connected is becoming more and more evident. It is fairly obvious that the new knowledge and discoveries arise on the dividing line between the different fields and disciplines of science. In the last few decades, the human society has reached the new qualities of civilization. This applies, in particular, for the disciplines of science and their applications; however, this statement can hardly be used with reference to the moral and ethical aspects of the human lives. At present, the biomedical science is a wide-ranging interdisciplinary science which, in case of lack of cooperation with other scientific disciplines, would be condemned to stagnation. That is the reason why the SCT is aimed at integrating the specialists both within the biomedical science and within the engineering fields.

The priority objective of the SCT is to present the professional public and specialists involved in the clinical practice with the latest knowledge in the field of connective tissues. The SCT is also a civic society whose aim is to bring people close together by joining members of the clinical staff, researchers and teachers including the retired ex-colleagues and, last but not least, the undergraduates and PhD students from universities and academic establishments.

The SCT is planning to organize at least two professional and social meetings each year. Beside the professional contribution of these meetings, emphasis will be laid on social activities – informal discussions of all those who do not want to stagnate and who do not want to acquire the new knowledge in solitary confinement.

**The annual membership fee is 200 Czech crowns for full workers, and 100 Czech crowns for students and pensioners.** This membership fee shall be used to cover the basic costs on correspondence with the members of the Society in order to inform them about organizing colloquiums, symposiums and social meetings.

The SCT is also engaged in publishing of the interdisciplinary journal entitled *Locomotor System – Advances in Research, Diagnostics and Therapy*. You are invited to contribute to the journal writing professional articles, exchanging experience or, simply sharing your opinions. **The annual subscription is 240 Czech crowns, for foreign subscribers 12 euros** (incl. shipping).

**Dear Colleagues, do not stand aside (suffering from terrible lack of time) and join the professional people in the field of connective tissues to whom you undoubtedly belong. In this beautiful country, the sources of knowledge should be kept alive and maintained permanently. Our role in this process is not accidental. We are much**

**obliged to our ancestors who had developed the qualities of proficiency in this country. Do not allow the decline of science. Do not let the programmed indifference arising from lack of professionalism, enviousness, and pathological promotion of economic and power interests manipulate us.**
**We are looking forward to meeting you. We will be pleased if you join us and share your experience with us.**

**On behalf of the committee of the Society for connective tissues:**

**Associate Professor Ivo Mařík, MD, PhD** – chairman
**Professor Josef Hyánek, MD, DrSc** – vice-chairman
**Professor Miroslav Petrtýl, MSc, DrSc** – research secretary
**Hana Hulejová, MSc** – secretary
**Jana Zelenková, Eng.** – treasurer

Society for Connective Tissue CMA J. E. Purkyně
&
Czech Society for Prosthetics and Orthotics CMA J. E. Purkyně
&
Ambulant Centre for Defects of Locomotor Apparatus

**invite you for**

# THE 9TH PRAGUE-SYDNEY-LUBLIN SYMPOSIUM AND 12TH KUBÁT'S PODIATRIC DAY

# "NEWS IN DIAGNOSTICS AND COMPREHENSIVE TREATMENT OF LOCOMOTOR DEFECTS"

The Symposium is launched within the framework Bone and Joint Decade 2000–2010 and belongs to education actions integrated into the life training system of physicians.

The Symposium will be held on 19th–20th October 2007 from 9 a.m. at The Medical House, Sokolská 31, 120 26 Prague 2, Czech Republic.

**Registration Form** should contain: Name, Address, Phone, Fax, E-mail.
**Extended Abstract Form** with key words (try to provide objectives, methods, results and discussion, English is preferred) – **submission deadline: July 31, 2007.**

Conference fee 200 Czech crowns (approx. 10 Euro) will be paid during registration. Participants will receive the journal "Locomotor System" with programme and extended abstracts of lectures.

Both Forms submit by e-mail: ambul_centrum@volny.cz
Assoc. Prof. Ivo Mařík, M.D., PhD., Ambulant Centre for Defects of Locomotor Apparatus, Olšanská 7, 130 00 Praha 3, Tel./fax: +420 222 582 214, Czech Republic

# PLÁNOVANÉ AKCE OSTEOLOGICKÉ AKADEMIE ZLÍN NA ROK 2007

# SCHEDULED ACTIONS OF THE OSTEOLOGIC ACADEMY OF ZLÍN FOR THE YEAR 2007

*připravuje / prepares*

## PRACOVNÍ DEN 27. KVĚTNA VE ZLÍNĚ

## WORKSHOP-SEMINAR ON MAY 27, 2007, IN ZLIN

**Program:**
Osteologická antropologie / Osteologic anthropology
Novinky v pediatrické denzitometrii / Advancements in pediatric densitometry

## PRACOVNÍ DEN 24. LISTOPADU VE ZLÍNĚ

## WORKSHOP-SEMINAR ON NOVEMBER 24, 2007, IN ZLIN

**Program:**
Laboratorní a klinická genetika v osteologické praxi / Laboratory and clinical genetics in osteologic practice
Základní otázky biomechaniky v osteologické praxi / Basics of biomechanics in osteologic practice

*podílí se na organizaci a programu / co-organize*

## KONGRES SMOS A SOMOK

## CONGRESS WITH SMOS AND SOMOK

ve dnech 28.-30. října 2007 v Luhačovicích
on October 28-30, 2007, in Luhacovice

# ZPRÁVA O ČINNOSTI ČESKÉ SPOLEČNOSTI ANTROPOLOGICKÉ V ROCE 2006

Viničná 7, 128 44 Praha 2
www. anthropology.cz

Hlavní výbor ČSA se v roce 2006 sešel v únoru, červnu a listopadu na třech schůzích. Na únorové schůzi výbor rozhodl o zvýšení členských příspěvků ze stávajících 200 Kč/rok, na 300 Kč/rok, s platností od roku 2007. Schválení zvýšení příspěvků proběhlo formou hlasování na schůzích jednotlivých poboček ČSA (Brno – 28. 2., Olomouc – 6. 4., Praha – 7. 6. 2006). Členové Společnosti byli koncem června o této skutečnosti vyrozuměni osobním sdělením.

V březnu 2006 vyhlásil hlavní výbor ČSA, společně s Městským úřadem v Humpolci, další ročník **„Ceny dr. A. Hrdličky pro mladé antropology“,** v kategorii doktorských disertačních prací. Uzávěrka přihlášek byla stanovena na 31. října 2006. Práce, přihlášené do minulého ročníku, ve kterém nebyla pro malý počet přihlášek tato kategorie hodnocena, jsou automaticky přijaty do nového kola. Na listopadové schůzi hlavního výboru ČSA byli, pro posouzení jednotlivých disertací, stanoveni oponenti. Vyhlášení výsledků soutěže proběhne v průběhu roku 2007.

Za podpory grantové dotace RVS vyšlo počátkem roku další číslo **„České antropologie“** za rok 2005, v srpnu pak i **Supplementum** s abstrakty z **„13. antropologických dnů“** a 7. mezinárodní **konference „Diagnostika pohybového systému“,** které uspořádala olomoucká pobočka společně s Fakultou tělesné kultury UP v Olomouci. Hlavní výbor ocenil práci výkonné redaktorky časopisu Prof. RNDr. Jarmily Riegerové, CSc. **„Česká antropologie“** pod její edicí získala výrazně na prestiži. Časopis vychází ve velmi reprezentativním provedení a díky nově sestavené redakční radě jsou publikovány kvalitní příspěvky. Anglické abstrakty jednotlivých příspěvků budou, pro dostupnost širší veřejnosti, uveřejňovány i na webových stránkách ČSA. Plánováno je i vytvoření elektronické formy tohoto časopisu. K předepsanému říjnovému termínu podal hlavní výbor na Radu vědeckých společností žádost o dotaci na podporu vydání časopisu ČSA a provoz webových stránek pro rok 2007.

ČSA má opětovné zastoupení v koncilu Evropské antropologické asociace. Na 15. kongresu EAA v Budapešti, který se konal ve dnech 31. 8.–3. 9. 2006, byl znovu zvolen Doc. RNDr. Pavel Bláha, CSc. do funkce viceprezidenta.

Na listopadové schůzi schválil hlavní výbor návrhy pokladní ČSA na vyloučení některých členů, kteří dlouhodobě neplatí členské příspěvky a nereagují na opakované výzvy o doplacení dluhu.

V roce 2006 bylo přijato 10 nových členů – 5 olomoucká pobočka, 3 pražská pobočka, 2 brněnská pobočka.

## Pražská pobočka České společnosti antropologické

V roce 2006 uskutečnila pražská pobočka ve spolupráci s Antropologickým oddělením Národního muzea, Antropologickým sborem Společnosti Národního muzea a Katedrou antropologie a genetiky člověka Přírodovědecké fakulty UK, přednáškový cyklus s názvem **„Ženy v antropologii“.** Tento cyklus představoval poděkování ženám, které přispěly k rozvoji české antropologie, a to nejen těm, které tento obor vystudovaly, ale i těm, které jako manželky antropologů jim vytvářely vhodné podmínky pro jejich práci a měly tak na rozvoji tohoto oboru u nás nemalý podíl. Příkladem byly manželky profesorů Matiegky, Malého, Fettera, Valšíka, Absolona nebo Jelínka.

Cyklus zahájil Doc. RNDr. Milan Stloukal, DrSc. a uzavřel vedoucí Katedry antropologie a genetiky člověka PřF UK Prof. RNDr. Zbyněk Šmahel, CSc. Byl rozdělen do 4 večerů v období od 11. 5. do 8. 6. 2006. Přednášeli a moderovali Doc.RNDr. Miroslav Prokopec, DrSc. a prof.h.c. RNDr. Josef Wolf, CSc.

První večer byl věnován vzpomínce na ženy, které již nežijí. Po uvedení jejich biografie a zásluh byla osobnost jednotlivých žen dokreslena doplňky a připomínkami z pléna. Druhý večer měl název „Poděkování zasloužilým“. Prezentovány byly ženy, které svou prací přispěly k povznesení oboru a v současné době jsou již většinou v důchodu. Třetí a čtvrtý večer byl oslavou a blahopřáním ženám v antropologii, které v současné době v oboru pracují, ať již na přírodovědeckých nebo lékařských fakultách, výzkumných pracovištích, muzeích, jakož i na pracovištích příbuzných oborů, jako je např. archeologie nebo hygiena. Byly zmíněny i čerstvé absolventky oboru, nebo ty, které dosud studují k získání vyšší kvalifikace. Některá jména, uvedená na programu, byla příliš čerstvá na to, aby byla ve všeobecném povědomí. Museli pomoci v publiku přítomní pedagogové a školitelé doktorandů, aby se o každé ženě, uvedené v seznamu, mohlo říci kde pracuje a jakou problematikou se zabývá.

Cyklus ukázal, jaké má česká antropologie bohatství v ženách, které se podílely nebo podílejí na jejím rozvoji. Některé absolventky však nacházejí uplatnění mimo obor, který vystudovaly.

Součástí činnosti pražské pobočky bylo uspořádání výstavy fotografií pod názvem **„Tváře Indie“,** kterou instalovala, na návrh ředitele Chodovské tvrze p. Ing. Vladimíra Levického, kulturní referentka Martina Horáková v budově radnice Úřadu městské části Praha 11 od 5. 6. do 22. 6. 2006. Autor vystavených snímků Doc. M. Prokopec byl dvakrát v Indii. V r. 1963–64 jako antropolog na pozvání Indického statistického ústavu a v r. 1978–79 jako účastník Mezinárodního kongresu antropologických a etnologických věd. Pestrost a různorodost obyvatelstva zachytil na snímcích z každodenního života z mnoha různých míst země – zeměpisně od Bombaje po Kalkatu a od podhůří Himálaje po Maysor, a společensky od audience u presidenta v jeho paláci v Dillí po chudinské čtvrtě Kalkaty a domorodé kmeny v horách v poříčí řeky Krishna u Hyderabadu a v lesích Urisy. Nechybí ani záběry ze sídel maháradžů, ani typy lidí z pohraniční oblasti NEFA, z Manipuru, ze států Uttarpradéš, Maharástra, či z měst Poony, Barody, Puri, Bhubaneshwaru aj. ze současnosti, často na pozadí památek staleté kultury.

Výstavu zahájila starostka Prahy 11 pí. Marie Šorfová a Prof. PhDr. Rudolf Veselý, CSc. Pro časopis Photo Art ji komen-

toval Prof. PhDr. Ludvík Baran, CSc. Série snímků obyvatel Indie byla přenesena na CD a bude k disposici zájemcům na internetových stránkách České společnosti antropologické.

## Brněnská pobočky České společnosti antropologické:

Na první členské schůzi brněnské pobočky, která se konala 28. února 2006, byl jednomyslně schválen návrh hlavního výboru o zvýšení členského poplatku. V hlavním programu setkání vystoupila RNDr. Pavla Šťastná, Ph.D. z Technologické fakulty Univerzity Tomáše Bati ve Zlíně s přednáškou na téma **„Zdravotní potíže nohou současné populace jako důsledek nošení nevhodné obuvi“,** která se setkala s velmi příznivým ohlasem.

V březnu se konala výstava fotografií RNDr. Ladislavy Horáčkové, Ph.D. **„Mezinárodní expedice v Sakkáře – Egypt“** v Moravském zemském muzeu v Brně, v dubnu se tatáž výstava uskutečnila v Moravské zemské knihovně v Brně. Výstava nabídla návštěvníkům pohled českého antropologa na výzkumnou činnost v jedné z nejstarších egyptských nekropolí.

24. října se konala další členská schůze, na níž členové pobočky informovali o účasti na antropologických konferencích v Olomouci, Budapešti a v Řecku. Své poznatky a postřehy doplnili zajímavou fotodokumentací. Hlavním bodem programu se stala přednáška docenta Petra Hlaváčka ze zlínské Technologické fakulty Univerzity Tomáše Bati o posledních výzkumech obuvi terakotové armády Prvního svrchovaného císaře Čchinů.

Možnost setkávání mají členové brněnské pobočky již tradičně i na seminářích, které pro své studenty a členy ČSA pořádá Katedra antropologie Přírodovědecké fakulty MU.

V roce 2006 tak měli například možnost vyslechnout přednášky:

- Prof. PhDr. Josef Unger, CSc.: **Pohřební ritus 1. až 20. století v Evropě z antropologicko-archeologické perspektivy.**
- Doc. PhDr. Luboš Bělka, CSc.: **Santalový Buddha.**
- Prof. MUDr. Pavel Bravený, CSc., Doc. MUDr. Marie Nováková, Ph.D.: **Fyziologie krevního oběhu.**
- Doc. PhDr. Břetislav Vachala, CSc.: **Abúsír: Staroegyptské královské pohřebiště.**
- Doc. PhDr. Luboš Bělka, CSc.: **Buddhistické pojetí pekel.**
- Prof. PhDr. MgA. Miloš Štědroň, CSc.: **Mozart: antropologický přístup.**
- Mgr. Richard Thér: **Keramická technologie jako socio-kulturní fenomén: komplexní přístup ke studiu keramiky z mladší doby bronzové.**
- Prof. PhDr. Josef Unger, CSc.: **Školní antropologicko-archeologický výzkum pravěkého a slovanského pohřebiště v Divákách (u Hustopečí) Ústavu antropologie Přírodovědecké fakulty Masarykovy univerzity: výsledky výzkumu 2000–2006.**
- Doc. PhDr. Luboš Bělka, CSc.: **Šambhalský mýtus.**
- Prof. RNDr. Ivo Budil, Ph.D., DSc.: **Vývoj etnických a rasových vztahů v Jižní Africe v devatenáctém století.**
- Ing. Marie Dohnalová, CSc.: **Czechkid: multikulturalita očima dětí.**

## Olomoucká pobočka České společnosti antropologické

Olomoucká pobočka se sešla na čtyřech schůzích, na kterých její členové vzpomenuli náhlé úmrtí RNDr. Václava Hajna, CSc., dlouholetého člena olomoucké pobočky ČSA, oslavili životní jubileum Prof. RNDr. S. Komendy, DrSc. a vyslechli řadu odborných přednášek, např. **„Kulturní antropologie v Kazachstánu očima zdravotně-sociálního pracovníka“, „Symbolika sandálů na byzantských ikonách“** a další.

Členové olomoucké pobočky se podíleli na organizaci 13. antropologických dnů na téma **„Člověk – téma věčně živé“,** konané v Olomouci, odborně i organizačně zajišťovaných Katedrou funkční antropologie a fyziologie Fakulty tělesné kultury Univerzity Palackého. Anglická abstrakta příspěvků jsou publikována v Supplementu, Česká antropologie, 56, 2006.

Olomoucká pobočka dále spolupracovala na organizaci **„Festivalu zdraví a pohybu“,** který proběhl dne 3. 6. 2006 v Olomouci. Spolu s pracovníky Katedry antropologie a zdravovědy Pedagogické fakulty Univerzity Palackého zde bylo přítomným zájemcům prováděno antropometrické a fyziologické vyšetření, zaměřené na hodnocení výživového a zdravotního stavu (BMI, WHR, krevní tlak, množství tělesného tuku, orientační hodnocení zdatnosti oběhového systému).

RNDr. Petr Sedlak, Ph.D.
předseda ČSA

# PEDAGOGICKÁ FAKULTA UNIVERZITY PALACKÉHO V OLOMOUCI

**Katedra antropologie a zdravovědy a Katedra biologie**

ve spolupráci

s Českou antropologickou společností
&
s Českou společností entomologickou,
&
Krajskou hygienickou stanicí v Olomouci
&
a Zdravotním ústavem se sídlem v Olomouci

**pořádají ve dnech 5. – 6. září 2007 v Olomouci**

**mezinárodní vědeckou konferenci**

# I. OLOMOUCKÉ DNY ANTROPOLOGIE A BIOLOGIE

**pod záštitou děkanky Pedagogické fakulty UP v Olomouci prof. PaedDr. Libuše Ludíkové, CSc.**

# VŠEOBECNÉ INFORMACE

## Cíle konference

1. Prezentovat nové poznatky v oborech biologická antropologie, kulturní a sociální antropologie, zoologie a botanika.
2. Diskutovat působení environmentálních faktorů na vývoj a zdravotní stav obyvatelstva v Evropě.
3. Navzájem se informovat o interdisplinárních vztazích člověk – příroda – sociální prostředí.
4. Navrhnout využití přednesených teoretických a praktických poznatků do pedagogického procesu na základních, středních a vysokých školách.

## Hlavní garant konference

Doc. PaedDr. Miroslav Kopecký, Ph.D.

## Vědecký výbor

**Prof. RNDr. J. Riegerová, CSc.,**
vedoucí Katedry funkční antropologie a fyziologie FTK UP v Olomouci, ČR
**Prof. RNDr. Z. Šmahel, CSc.**
vedoucí Katedry antropologie a genetiky člověka, PřF UK v Praze, ČR
**Prof. PaedDr. L. Jančoková, CSc.**
Katedra telesnej výchovy a športu,
FHV Univerzity Mateja Bela v Banskej Bystrici, SR
**Doc. RNDr. P. Bláha, CSc.**
viceprezident koncilu Evropské
antropologické asociace, Katedra
antropologie a genetiky člověka,
PřF UK v Praze, ČR
**RNDr. P. Sedlak, Ph.D.**
předseda ČSA, Katedra antropologie
a genetiky člověka, PřF UK v Praze, ČR
**Doc. Ing. M. Bocáková, Ph.D.**
vedoucí Katedry biologie PdF UP
v Olomouci, ČR
**Doc. RNDr. J. Šteigl, CSc.**
vedoucí Katedry antropologie
a zdravovědy PdF UP v Olomouci, ČR
**Doc. RNDr. A. Pouličková, CSc.**
Katedra botaniky PřF UP v Olomouci, ČR

**MUDr. Z. Nakládal**
Krajská hygienická stanice Olomouckého kraje se sídlem v Olomouci, ČR
**RNDr. D. Dvorská**
ředitelka Zdravotního ústavu se sídlem v Olomouci, ČR

## Organizační výbor

*Předseda:*
**Doc. PaedDr. M. Kopecký, Ph.D.**
Katedra antropologie a zdravovědy PdF UP
*Tajemník:*
**PhDr. H. Skarupská, Ph.D.**
Katedra antropologie a zdravovědy PdF UP
*Členové:*
**Doc. Ing. M. Bocáková, Ph.D.**
Katedra biologie PdF UP
**Doc. RNDr. L. Hrabí, Ph.D.**
Katedra biologie PdF UP
**Doc. RNDr. L. Krejčovský, CSc.**
Katedra antropologie a zdravovědy PdF UP
**PhDr. I. Knausová, Ph.D.**
Katedra antropologie a zdravovědy PdF UP
**MUDr. H. Kabátová**
Krajská hygienická stanice v Olomouci
**MUDr. S. Jakubalová**
Zdravotní ústav se sídlem v Olomouci
**RNDr. V. Tlusták, CSc.**
Katedra biologie PdF UP
**Ing. I. Machar, Ph.D.**
Katedra biologie PdF UP
**Mgr. M. Müllerová**
Katedra biologie PdF UP

## Sekretariát konference

**Mgr. Jitka Tomanová**
Katedra antropologie a zdravovědy
Pedagogická fakulta UP v Olomouci
Žižkovo nám. 5, 771 40 Olomouc
tel.: 723 27 23 50
e-mail: Jitka.Tomanova@seznam.cz

## Prezentace na konferenci

Výsledky práce účastníků konference budou prezentované formou:
- plenárních přednášek
- referáty v příslušných odborných sekcích
- posterů
- praktických ukázek výuky

Odborné sekce:
- Biologická antropologie (garant Doc. RNDr. L. Krejčovský, CSc.)
- Kulturní a sociální antropologie (garant PhDr. I. Knausová, Ph.D.)
- Výchova ke zdraví (garant MUDr. H. Kabátová)
- Botanika (garant RNDr. V. Tlusták, CSc.)
- Zoologie (garant Ing. I. Machar, Ph.D.)
- Ekologie a ekologická výchova (garant Mgr. M. Müllerová)
- Didaktika biologie (garant Doc. RNDr. L. Hrabí, Ph.D.)

Oficiálními jednacími jazyky konference jsou: čeština, slovenština, polština a angličtina.

## Délka referátů

Hlavní přednášky 20 min., referáty v příslušných sekcích 10 min. a 5 min. na diskusi.

## Rámcový program konference

**Středa 5. 9. 2007**

| | |
|---|---|
| 9,00 – 10,30 hod. | prezentace účastníků |
| 10,30 – 12,30 hod. | zahájení konference a plenární přednášky |
| 12,30 – 14,00 hod. | oběd |
| 14,00 – 16,00 hod. | jednání v sekcích |
| 16,00 – 16,30 hod. | přestávka |
| 16,30 – 18,30 hod. | jednání v sekcích |
| 18,45 – 19,45 hod. | prohlídka Arcidiecézního muzea v Olomouci* (pro zájemce) |
| 20,00 hod. | večeře a společenský večer s hudbou |

**Čtvrtek 6. 9. 2007**

| | |
|---|---|
| 8,30 – 10,00 hod. | jednání v sekcích |
| 10,00 – 10,30 hod. | přestávka |
| 10,30 – 12,00 hod. | jednání v sekcích |
| 12,15 – 12,45 hod. | slavnostní zakončení |
| 13,00 – 14,00 hod. | oběd |
| | Návštěva nízkoenergetické budovy ve Sluňákově** (pro zájemce) |

*** Návštěva Arcidiecézního muzea v Olomouci**

1. června 2006 byl slavnostně zpřístupněn areál Arcidiecézního muzea, jediného tohoto typu v České republice, dokumentující stavební a umělecký vývoj Olomouckého hradu v průběhu celého tisíciletí, od pozůstatků paláců biskupského a knížecího přes románské, gotické a renesanční etapy až po pozdně barokní a rokokové interiéry. Vstup je pro účastníky konference zdarma.

**** Návštěva nízkoenergetické budovy ve Sluňákově**

Pro zájemce konference bude podle počtu přihlášených zorganizována ve čtvrtek 6. 9. 2007 exkurze do nově otevřeného střediska ekologické výchovy s oficiálním názvem „Centrum ekologických aktivit". Unikátní nízkoenergetická budova, postavená z podpory Státního fondu životního prostředí (SFŽP) a okolní přírodní areál nabízí především výukové programy (jednodenní i vícedenní – pobytové) pro základní i střední školy Olomouckého kraje, zaměřené na ekologii, environmentální výchovu a přírodopis. Sluňákov pořádá i výukové programy a semináře pro učitele a lektory ekologické výchovy. Protože Sluňákov leží u „vstupní brány" naučné cyklostezky do chráněné krajinné oblasti (CHKO) Litovelské Pomoraví, je zde v provozu návštěvnické informační centrum CHKO. Viz www.slunakov.cz

Doprava bude zajištěna autobusem. Čas exkurze bude upřesněn podle počtu přihlášených účastníků.

## Publikace

Účastníci konference budou informováni o přednesených referátech formou anotací i plnými texty příspěvků, které budou zveřejněny v **recenzovaném sborníku v elektronické podobě (CD-R)**. Podmínkou zveřejnění příspěvku bude zaplacení konferenčního příspěvku.

Pro psaní anotací a příspěvků do sborníku se prosím řiďte podle následujících instrukcí:

## Instrukce pro napsání anotace

1. Formát stránky: A 4, okraje 2,5 cm.
2. Písmo: Times Roman CE, 12 pt, bez dělení slov, hladký text.
3. Odstavec: řádkování jednoduché, zaro nání do bloku.
4. Anotace je v českém a anglickém jazyku.
5. Název anotace velkými písmeny, vycentrovat na střed.
6. Autoři: celé jméno, příjmení (bez titulů) a pracoviště (katedra, fakulta, škola, adresa, kontakt). Autoři z více pracovišť jsou rozlišeni horním indexem s odkazem na příslušné pracoviště.
   Příklad:
   Pavel Janák[1], Jiří Bezděk[2]
   [1] Katedra somatologie...
   [2] Státní zdravotní ústav....
7. Anotace v rozsahu maximálně 15 řádků a 5 klíčových slov.

## Instrukce pro psaní příspěvku

### Požadavky na digitální zpracování rukopisu do sborníku

1. Formát stránky: A 4, okraje 2,5 cm.
2. Písmo: Times Roman CE, 12 pt, bez dělení slov, hladký text.
3. Odstavec: řádkování jednoduché, zarovnání do bloku.
4. Název příspěvku česky a anglicky tučně velkými písmeny, vycentrovat na střed.
5. Autoři: celé jméno, příjmení (bez titulů) a pracoviště (katedra, fakulta, škola,adresa, kontakt). Autoři z více pracovišť jsou rozlišeni horním indexem s odkazem na příslušné pracoviště.
   Příklad: Pavel Janák[1], Jiří Bezděk[2]
   [1] Katedra somatologie...
   [2] Státní zdravotní ústav....
6. Text příspěvku členěte na následující oddíly: Úvod, Cíl práce, Metodika, Výsledky a diskuse, Závěr, Literatura. Nadpisy uvedených oddílů Times Roman CE, 12 pt, tučně.
7. Tabulky a grafy ve formátu MS WORD a EXCEL. Nadpis u tabulek, grafů a obrázků nezkráceně, není ukončen tečkou. (Příklad: Tabulka 1 Porovnání tělesné výšky 7 – 15letých chlapců a dívek (cm). Pokud bude v textu odkaz na tabulku, graf a obrázek, uvádějte odkaz následujícím způsobem: ... uvedené hodnoty převyšují doporučená kritéria (Tabulka 1, Graf 1) nebo ... tabulka 1 a graf 1 uvádějí hodnoty, které převyšují doporučená kritéria.
8. Tabulky, grafy a obrázky mohou být uvedeny v textu nebo i na závěr příspěvku za literaturou.
9. Tabulky: písmo Times Roman 12 pt, řádkování jednoduché. Grafy: písmo Times Roman 12 pt.
10. Rovnice, matematické vzorce a speciální znaky vkládejte do textu jako objekt Microsoft Equation 3.0 – editor rovnic.
11. Referenční seznam, uvedený pod nadpisem Literatura je seřazen podle abecedního pořádku. Citace literárních zdrojů je podle ČSN ISO 690 podle níže uvedených příkladů:

**1. učebnice, monografie, studijní texty**
HAAG, H., GRUPE, D., KIRSCH, A. *Sport Science in Germany*.
Berlin: Verlag Heidelberg, 1972. 575 p. ISBN 3-540-55657-5.

**2. časopis**
JANÁK, P., BEZDĚK, J. Hodnocení klenby nohy pomocí různých plantografických metod u dívek ve věku 7-19 let. *Česká antropologie.* Olomouc: Univerzita Palackého, 2003, roč. 53, s. 47-51. ISSN 0862-5085.

**3. sborník**
BEZDĚK, J., JANÁK, P. Výchova ke zdraví jako nový studijní obor na PdF UP v Olomouci. In A. Suchomel (ed.) *Sborník z mezinárodní vědecké konference „Tělesná výchova*

*a sport 2004, Liberec – Euroregion Nisa".* Liberec: Technická univerzita, 2004. s. 145–151. ISBN 80-7083-901-5.

**Při prezentaci odevzdejte v tištěné podobě anotaci i plný text, do kterého jsou zařazeny tabulky, grafy a obrázky** nebo zašlete na uvedenou adresu sekretariátu konference a to v jednom výtisku a na disketě nebo CD-R ve formátu MS WORD 97, 2000 a 2003 pro Windows.

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**Pro odevzdání příspěvku do sborníku je stanoven termín 6. 9. 2007. Příspěvky, které nebudou do tohoto termínu předány, nebudou publikovány.**
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## ORGANIZAČNÍ POKYNY

### Datum konání

5. a 6. 9. 2007

### Konferenční poplatek

500 Kč, studenti 250 Kč, učitelé ZŠ a SŠ neplatí konferenční poplatek.

### Ubytování a stravování

ubytování bude zajištěno na VŠ kolejích v místě konání konference v ceně 105 Kč/osoba nebo 210 Kč osoba/samostatný pokoj. Snídaně zajištěna v místě ubytování v ceně 60 Kč. Oběd v ceně 130 Kč a společenský večer 250 Kč (jídlo a hudba).

Veškeré platby, konferenční poplatek a poplatky za ubytování, stravu a společenský večer bude hrazen hotově v den zahájení konference nebo platbou poukázat na účet (doporučujeme platbu mezinárodní poštovní složenkou).

**Adresát:** Univerzita Palackého v Olomouci
Pedagogická fakulta, Žižkovo nám. 5, 771 40 Olomouc
**Číslo účtu:** 19-1096330227/0100
**IBAN:** CZ0901000000191096330227
**Variabilní symbol:** 99410371
**Konstantní symbol:** 0308
**Peněžní ústav:** Komerční banka Olomouc
Tř. Svobody 14, 779 11 Olomouc

**SWIFT (kód banky):** KOMBCPPXXX

## Místo konání

Pedagogická fakulta PdF UP v Olomouci, Žižkovo nám. 5, Olomouc 771 40
Z hlavního vlakového nádraží tramvají směr Centrum vystoupit na 2 zastávce na Žižkově náměstí.

Parkování účastníků konference bude zajištěno v prostorách Pedagogické fakulty UP v Olomouci v místě konání konference.

**Přihlášku na mezinárodní vědeckou konferenci I. Olomoucké dny antropologie a zdravovědy konané ve dnech 5.–6. 9. 2007 zašlete nejpozději do 10. 5. 2007.**

**Objednávku na ubytování a stravování na I. Olomoucké dny antropologie a zdravovědy konané ve dnech 5.–6. 9. 2007 zašlete nejpozději do 10. 5. 2007.**

# PŘIHLÁŠKA NA MEZINÁRODNÍ VĚDECKOU KONFERENCI

| **Údaje o účastníku konference** | | | |
|---|---|---|---|
| Příjmení, jméno, tituly: | | | |
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| Telefon, e-mail adresa: | | | |
| **Příspěvek na konferenci** | | | |
| Autor, autoři: | | | |
| Název příspěvku česky a anglicky: | | | |
| **Forma prezentace (označte X)** | | | |
| Plenární přenáška | ☐ | Přednáška v odborné sekci | ☐ |
| Poster | ☐ | Praktická prezentace (laboratoř) | ☐ |
| **Odborná sekce (příslušnou sekci označte X)** | | | |
| Biologická antropologie | ☐ | Zoologie | ☐ |
| Botanika | ☐ | Výchova ke zdraví | ☐ |
| Didaktika biologie | ☐ | Ekologická výchova | ☐ |
| Kulturní a sociální antropologie | ☐ | | |
| **Nároky na didaktickou techniku a pomůcky (označte X)** | | | |
| Dataprojektor | ☐ | Diaprojektor | ☐ |
| Zpětný projektor | ☐ | | |
| Laboratoř (specifikovat přístroje a pomůcky) | | | |
| | | | |
| Jiné (napsat) | | | |
| | | | |
| **Mám zájem se účastnit návštěvy (označte X)** | | | |
| Arcidiecézního muzea | | | ☐ |
| Nízkoenergetické budovy ve Sluňákově | | | ☐ |

Přihlášku zasílejte v elektronické podobě na e-mailovou adresu:
**Jitka.Tomanova@seznam.cz**
nebo vytištěnou na adresu **Mgr. Jitka Tomanová, Katedra antropologie a zdravovědy, Pedagogická fakulta Univerzity Palackého, Žižkovo nám. 5, 771 40 Olomouc.**

# OBJEDNÁVKA NA UBYTOVÁNÍ A STRAVOVÁNÍ

| **Údaje o účastníku konference** | | |
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| **Snídaně** | | |
| Středa 5. 9. 2007 | 60 Kč ☐ | |
| Čtvrtek 6. 9. 2007 | 60 Kč ☐ | |
| Pátek 7. 9. 2007 | 60 Kč ☐ | |
| **Oběd** | | |
| Středa 5. 9. 2007 | 130 Kč ☐ | |
| Čtvrtek 6. 9. 2007 | 130 Kč ☐ | |
| **Ubytování** | | |
| Ze dne 4. 9. na 5. 9. 2007 | 1 lůžko 105 Kč ☐ | samostatný pokoj 210 Kč ☐ |
| Ze dne 5. 9. na 6. 9. 2007 | 1 lůžko 105 Kč ☐ | samostatný pokoj 210 Kč ☐ |
| Ze dne 6. 9. na 7. 9. 2007 | 1 lůžko 105 Kč ☐ | samostatný pokoj 210 Kč ☐ |
| **Společenský večer** | | |
| Středa 5. 9. 2007 | 250 Kč ☐ | |
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# KONFERENCE: XX FECTS MEETING 1. 7.–5. 7. 2006 OULU, FINSKO

**BRAUN M., HULEJOVÁ H.**

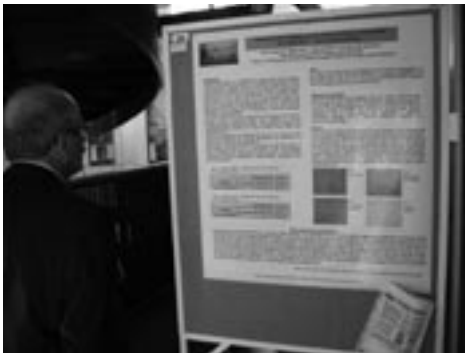
Revmatologický ústav, Praha

V letošním roce se konal již výroční XX. ročník setkání Federace evropských pojivových společností (FECTS). Tato konference se koná v posledních letech každé 2 roky – již tradičně počátkem července. Své účastníky hostilo tentokrát finské Oulu – město ležící na 65. rovnoběžce, poblíž severního polárního kruhu na břehu Botnického zálivu. Toto město s nejseverněji položenou univerzitou na světě a bohatou historií, jež v loňském roce oslavilo 400 let od svého založení, je dnes synonymem pro centrum moderních technologií a špičkový výzkum.

Spolupořadatelem FECTS byla tento rok Mezinárodní společnost biologie pojiva (ISMB) a všechny přednášky probíhaly společně v moderně vybavených prostorách lékařského kampusu univerzity v Oulu (založena 1958), vzdáleného necelé 3 km od živého středu města.

V rámci zahájení odborného programu byla výborem ISMB udělena též cena pro mladé vědce „Rupert Timpl Prize“ za nejlepší publikaci z oblasti biologie pojiva za uplynulé 2 roky, následovaná přednáškou oceněné autorky (Elizabeth Canty).

Ve večerních hodinách proběhlo slavnostní uvítání účastníků spojené s bohatým rautem v historickém sále radnice města za účasti starosty Oulu a organizátorů konference. Ačkoli pro většinu účastníků byl jistě nezvykem, v této roční době a lokalitě právě kulminující polární den, účast i na dopoledních plenárních přednáškách (začínajících obvykle již před 9. hodinou ranní), bývala hojná. Po poledni pauze se návštěvníci konference rozešli dle svých zájmů až do 5 přednáškových sálů, kde se přibližně do 16. hodiny paralelně konaly specializované workshopy. Na tato krátká ústní sdělení, pak týž den navazovala prezentace posterů, tematicky odpovídajících problematice zastoupené na workshopech konkrétního dne. I zde byl zájem značný a živá diskuze zde probíhala přibližně do 6. hodiny večerní, kdy byl kyvadlovou dopravou zajištěn rozvoz účastníků zpět do hotelů.



Program rovnoměrně rozložil klíčová témata související s metabolismem pojivových tkání – počínaje biologickými a biochemickými aspekty až po genetické pozadí onemocnění pojiva. Značná pozornost byla tradičně věnována struktuře pojiva, funkci jednotlivých kolagenních typů a patologickým změnám v důsledku chorob pojiva. Hojně zastoupena byla i témata z oblasti buněčné biologie (buněčné mediátory, interakce a signalizace). Řada posterů a přednášek se týkala také remodelace pojiva a extracelulární matrix, novým proteinům, glykoproteinům a diagnostickým markerům metabolického obratu kosti i elastických tkání. Ve výzkumu pojiva jsme zaznamenali stále větší důraz na aplikace metod molekulární biologie a genového inženýrství. Část prezentovaných prací byla věnována i kazuistikám a novým terapeutickým postupům, včetně využití zvířecích modelů chorob pojiva.

Příjemné počasí, dlouhé večery s půlnočním sluncem a nevšedním množstvím světla stejně tak jako živý ruch v ulicích i v časných ranních hodinách udělalo spolu s přátelskou atmosférou a krásným přírodním prostředím Finska na účastníky jistě příznivý dojem což ještě umocnilo přínosný a hodnotný program odborný. Z jeho nejzajímavějších témat jsme pro Vás vybrali několik příspěvků, které Vám dáváme k dispozici za tímto úvodníkem a věříme, že i Vás některý z široké palety příspěvků zaujme a přiměje k účasti na dalším celoevropském setkání pojivových specialistů, na FECTS v roce 2008.

## TRAFFICKING, CELLULAR ASSEMBLY AND STRUCTURE OF COLLAGEN FIBRILS

Karl E. Kadler
Wellcome Trust Centre for Cell-Matrix Research, Faculty of Life Sciences, University of Manchester, UK

The goal of the Kadler laboratory is to understand how cells in tissues build an ECM comprising organised arrays of collagen fibrils. The 3-dimensional organisation of extracellular collagen fibrils is a major determinant of connective tissue function but how this is achieved is poorly understood. A prime example is the parallel arrangement of collagen fibrils in tendons that resist pulling forces. Collagen can be extracted from tendon and reconstituted into fibrils in vitro. However, even though the fibrils are identical in appearance to tendon fibrils they are disorganised. Moreover, cells in culture do not synthesise tissue. These observations suggest a multicellular involvement in the establishment of ECM organisation in vivo. The Kadler laboratory is using three research strands to understand the cell-mediated assembly of collagen fibrils in tissue. The first strand uses 3D electron microscopy to determine the trafficking of procollagen in embryonic tendon cells. This work has led to the discovery of two pathways of procollagen trafficking and a novel transport compartment, called a fibricarrier, that contains newly-formed collagen fibrils. The fibricarriers, which can be 14 um long in embryonic tendon cells, are targetted by the actin cytoskeleton to novel plasma membrane protrusions called fibripositors through which the fibrils are secreted. Interestingly, the fibripositors protrude into extracellular spaces between the cells. The second strand of research uses molecular biology, biochemistry and immunofluorescence approaches to determine how the spaces between the cells are generated and maintained. We have shown that cadherin-11

is a key component of adherens junctions between embryonic tendon cells. Moreover, we have identified a novel cell-cell junction expressed by epitenon cells (at the surface of the tendon) that contains ZO-1 and N-cadherin. These results show that tendon contains at least 3 distinct populations of cells that form a cellular scaffold on which the 3D organisation of the ECM is established. In a third strand of research we have used 3D electron microscopy to determine the medium resolution (~5 nm) structure of thin collagen fibrils in cartilage. The structure shows a unique 10+4 microfibrillar arrangement of collagen II, XI and IX molecules within the fibril. This new structure is consistent with existing biochemical and structural observations, and, for the first time, explains the genetic data obtained from collagen XI knock--out mice. The research was funded by The Wellcome Trust, the BBSRC (UK) and European Framework V.

**1.** CANTY E. G., LU Y., MEADOWS R. S., SHAW M. K., HOLMES D. F. and KADLER K. E. (2004): Co-alignment of plasma membrane channels and protrusions (fibripositors) specifies the parallelism of tendon. Journal of Cell Biology 165: 553–563.
**2.** STARBORG T., CANTY E. G., LU Y., MEADOWS R. S., HUMPHRIES S. M., HOLMES D. F., O'TOOLE E. and KADLER K. E. Clustering and progressive maturation of transport carriers in the fibripositor pathway. Submitted for publication.
**3.** RICHARDSON S. H., STARBORG T., MEADOWS R. S., LU Y., VERDI C. and KADLER K. E.: A novel role for cadherin-11 containing adherens junctions in extracellular matrix assembly. Submitted for publication.
**4.** HOLMES D. F., STARBORG T. and KADLER K. E.: A novel 10+4 microfibril structure of thin cartilage fibrils. Submitted for publication.

## THE $NH_2$-TERMINAL PROPEPTIDE OF TYPE I PROCOLLAGEN FUNCTIONS BOTH INTRA- AND EXTRACELLULARLY TO MODULATE CELL FUNCTION

Paul Bornstein
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The function of the $NH_2$-terminal propeptide of type I procollagen (N-propeptide) is poorly understood. We now show that a recombinant trimeric N-propeptide interacts with TGFβ1 and BMP2, as determined by co-immunoprecipitation experiments, and inhibits the function of both cytokines, as judged by cell culture-based assays. Furthermore, N-propeptide functions intracellularly since its synthesis by stably transfected COS-7 cells results in an increase in phosphorylation of Akt and Smad3, and is associated with a marked reduction in type I procollagen synthesis and impairment in adhesion. These effects are not observed when N-propeptide, or the culture medium from stably transfected, N-propeptide-expressing cells, is added to the culture medium of control COS-7 cells. Both the binding of N-propeptide to cytokines and its intracellular functional properties are entirely dependent on the presence of the exon 2-encoded globular domain. Our findings suggest that N-propeptide performs an important feedback regulatory function, and provide a rationale for the poorly understood prominence of a homotrimeric form of type I procollagen (α1 trimer) during vertebrate development.

## STRUCTURE AND FUNCTION OF TYPE IV COLLAGEN GENE PRODUCTS

Toshihiko Hayashi
Department of Pharmaceutical Sciences,
Teikyoheisei University, Ichihara, Chiba, Japan

The products of C0L4Aland COL4A2 genes function as a major component of basal lamina as a molecular entity of $[\alpha l(IV)_2]\alpha 2(IV)$. The type IV collagen isolated from bovine lens capsule or human placenta assembles into the polygonal meshwork structure with an average distance of branching points of 18 nm, which corresponds to the pore size of skeletal structure of basal lamina in vivo. Namely, the type IV collagen alone, in the absence of laminins or other basement membrane components, can form a fine meshwork structure, physiologically important as sieving blood proteins out. The lateral interactions of collagen triple-helix region that have some 20 interruptions of GXY repeats can theoretically form the fine meshwork structure reconstituted from the type IV collagen in addition to the interactions of 7S-7S regions, NCI-NCI regions, and NCI with triple-helical region.

Two different levels of structural and functional features of the type IV collagen gene products will be presented. 1. Gel or non-gel aggregates of type IV collagen polygonal meshwork. 2. Triple-helical molecules or non-triple helical polypeptides of $\alpha l(IV)$ and $\alpha 2(IV)$ chains.

The type IV collagen from bovine placenta in a physiological solution aggregates into a sheet-like structure with the polygonal meshwork structure at a room temperature or above (non-gel aggregates). The same solution forms gel when it is incubated at a lower temperature or on ice for days. Electron microscopic pictures can not distinguish the aggregate morphology whether they are in gel or in non-gel. However, aorta smooth muscle cells in culture show extremely different morphology whether the cells are on type IV collagen aggregates in gel form or in non-gel form. The cells are totally quiescent and expressing contractile phenotype on the type IV collagen gel, but the same cells proliferate on non-gel aggregates. Human aorta endothelial cells are maintained in a cobble stone-like structure for several months in the cell cultures with non-gel form of type IV collagen aggregates, whereas the endothelial cells do not spread on the gel form. Three-dimensional distribution of cell-interacting sites of type IV collagen could be crucial in affecting cell functions.

The second characteristic found for type IV collagen is conformation of the type IV collagen polypeptides. Cultured cells secrete non-helical $\alpha l(IV)$ and $\alpha t2(IV)$ chains under the conditions where type I procollagen is not secreted or when ascorbate level is reduced. The gelatin form of type IV collagen polypeptides can be isolated from human placenta and tumor tissues, indicating that the gelatin form may be involved in tissue remodeling. Most recently, evidence is obtained that the type XVIII collagen is also secreted as a gelatin form when the cells are cultured without ascorbate. The finding raises questions:

1. How are non-helical collagen polyppeptides secreted? 2. How can they survive proteolysis? Specific sugars attached to the gelatin form might be relevant.

## THE DEVELOPMENT OF RECOMBINANT HUMAN COLLAGENS AS BIOMATERIALS FOR TISSUE ENGINEERING AND OTHER MEDICAL USES

James W. Polarek, David Olsen, Chunlin Yang,
Robert Chang, and Scott Leigh
FibroGen Inc., South San Francisco, CA

Collagen, generally extracted from bovine and porcine tissues, is a widely used biomaterial. We have developed a scaled--up and highly productive recombinant production process for human collagen type III using *pichia pastoris* fermentation. Characterization of the recombinant material has been carried out by a variety of in vitro methods to analyze its structure and authenticity, as well as a number of in vivo analyses designed to test its performance as a replacement for the animal derived collagens. The safety of the material was first demonstrated in a series of in vivo and in vitro biocompatibility/toxicology studies as well as a human safety study. The objective of the clinical study was to evaluate the safety and tolerability of FG-5016, type III recombinant human collagen in healthy subjects. The study was an open-label, single-group, single center study involving 40 male and female subjects. Each subject received two intradermal injections of FG-5016 approximately 30 days apart. Subjects were assessed for safety and immune response. Safety was evaluated in terms of injection site reactions, systemic reactions, other adverse events, physical examinations, and laboratory tests. Blood samples were collected for measurement of IgG antibodies against rhCIII, *P. pastoris* mannan, and host cell protein.

## SUPRAMOLECULAR ASSEMBLIES OF THE EXTRACELLULAR MATRIX: ALLOYS, COMPOSITES AND AETWORKS

Peter Bruckner
Institute of Physiological Chemistry
& Pathobiochemistry,
University of Munster, Germany

Extracellular matrix macromolecules commonly are large multidomain proteins subject to extensive post-translational modifications, including the attachment of carbohydrates (glycoproteins, proteoglycans). Thus, they provide multiple opportunities for molecular interactions and, hence, are incorporated into large and highly ordered supramolecular aggregates (fibers and fibrils, microfibrils, networks, etc.). Rarely, if ever, such suprastructures consist of singe molecular species. Their heterotypic composition not only bestows onto them functional specificity by complexity but also results in tissue-specific molecular organizations of matrix assemblies closely tailored to their functional needs. The major molecular components thus do not single-handedly specify the physical and biological properties. Quite to the contrary, quantitatively minor species often impose to the entire aggregates distinct molecular organizations resembling alloys in many respects. For example, both, corneal stroma and tendons contain collagen I as the major structural macromolecule. However, collagen I co-polymerizes with distinct amounts of minor collagens and proteoglycans to generate sheets of parallel, monotonously thin, and poorly banded collagen fibrils or bundles of thick and strongly banded fibres, respectively. The incorporation of a component may be transitory to prevent or to afford rearrangements or fusion

of smaller aggregates into larger ones. The distinct types of cartilage collagen fibrils well illustrate this point. Macromolecular alloy, composite, or network characteristics specify discrete cellular responses controlled by appropriate cell-matrix-interactions. The principles guiding suprastructural specificity and its functional importance only begin to be unraveled.

## ADIPOKINES AND CRUCIATE LIGAMENT METABOLISM

Anderson V. M., Macrorv L. C., Innes J. F., Vaughan-Thomas
A Faculty of Veterinary Science,
University of Liverpool, UK

Rupture of the anterior cruciate ligament (ACL) and development of secondary osteoarthritis is a common orthopaedic problem in dogs. Body mass and obesity are thought to be risk factors for cruciate disease. Adipose tissue is the site of production for many hormones and cytokines including leptin and tumour necrosis factor-alpha (TNF-alpha). In this study we investigated the role of leptin and TNF-alpha on ACL metabolism. Leptin receptor (LEPR) mRNA is expressed by isolated ACL cells and intact ACL tissue. This finding was confirmed by Western blotting. mRNA extracted from cultured ACL cells was subjected to real-time PCR analysis, which showed that TNF-alpha increased ($p < 0.0001$) MMP-1 and MMP-3 expression, relative to GAPDH. HuR leptin (lOng/ml) did not have a significant effect on MMP mRNA expression alone or in combination with TNF-alpha. Zymography revealed that ACL cells produce proMMP-2 activity. However, neither MMP-9 nor MMP-2 could be detected. TNF-alpha treatment had no effect on gelatinase activity levels. Apart from the mechanical strain placed upon the cruciate ligament in situ, these studies suggest that obesity also increases the susceptibility of the ACL to cytokine-induced remodelling or degeneration.

## ALTERED TYPE XIII COLLAGEN EXPRESSION INTERFERES WITH OSTEOBLAST FUNCTION

Ylönen R.[1], Latvanlehto A.[1], Kyronlahti T.[1], Ilves M.[2], Lehenkan P.[3], Tuukkanen J.[4], Pihlajaniemi T.[1]
[1] Collagen Research Unit, Biocenter Oulu, Medical Biochemistry and Molecular Biology
[2] Department of Physiology, Biocenter Oulu
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Type XIII collagen is a type II transmembrane protein which is located in focal adhesions of cultured cells and in the adhesive structures of tissues. Sites of strong type XIII collagen expression include cartilage and bone. We have previously generated a transgenic mouse line overexpressing type XIII collagen. Use of a 1-kb Coll3al promoter linked with type XIII collagen cDNA sequences led to strong expression of the transgene in skeletal tissues resulting in massive increase in bone mass with high mineral density. Recently, two additional mouse lines, type XIII collagen knock-out (Coll3al-/-) and knock-in (Coll3alLacZ/LacZ) mice, have been generated by homologous recombination. The type XIII collagen promoter-driven LacZ expression was detected widely, but strong signals were found in developing and adult bone, more specifically in periosteal osteoblasts. These mice lacking type XIII collagen are smaller than with d-type littermates and their bones have reduced mechanical properties. To investigate the role of type XIII collagen in osteoblasts and

bone modeling we have generated primary osteoblast cultures from the transgenic mice. Overexpression of type XIII collagen in osteoblasts enhanced both cell proliferation and differentiation while lack of it had opposite effects. Furthermore, mutant cells responded to mechanical strain differently than wild-type cells. The findings suggest that type XIII collagen has an important role in bone modeling, and it may in particular have a function in coupling the regulation of bone mass to mechanical usage.

## COLLAGEN IX AND CHONDRODYSPLASIAS — MUTATIONS, REDUNDANCE AND DISEASE

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Chondrodysplasias are a diverse and genetically heterogeneous group of skeletal disorders, especially affecting endochondral ossification. The extracellular matrix protein collagen IX has been implicated in one of these diseases, namely multiple epiphyseal dysplasia (MED). Although the mutations leading to MED have already been identified, the mechanisms remain unclear. Therefore, we want to investigate the effects of these mutations on protein folding and trafficking as well as on chondrocyte viability and ECM assembly. First, cloning and expression of the alphal (IX) chain was established, allowing the purification of wildtype and mutant collagen IX alphal chain homotrimers for detailed biochemical analyses. To investigate the impact of mutated chains on cells, in vitro systems for transfection experiments had to be optimized. Secondly, we investigated the role of collagen IX in matrix assembly. Therefore, sternal murine chondrocytes isolated from wildtype mice as well as collagen IX and COMP deficient mice were stained for collagen II, collagen IX, COMP and matrilin-3, revealing a loss of matrilin-3 from the pericellular network. Additional studies on differences in the protein distribution confirmed an altered integration of matrilin-3 into the matrix of collagen IX deficient chondrocytes. To further elucidate the function of collagen IX in matrix assembly, double knock out mice deficient in both collagen IX and an identified interaction partner (e.g. matrilin-3, COMP) will be analyzed.

## COMP IS INVOLVED IN HUMAN LIMB DEVELOPMENT AND IN THE PATHOGENESIS OF OSTEOARTHRITIS

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As a member of the thrombospondin gene family, COMP is mainly found in the extracellular matrix often associated with cartilage tissue. COMP exhibits a broad binding repertoire and has been shown to be involved in the regulation of chondrogenesis in vitro. Not much is known about the role of COMP in human cartilage tissue in vivo. With the help of immunohistochemistry, Western blot, in situ-hybridization and real-time RT-PCR, we aimed to elucidate the role of COMP in embryonic human, healthy adult and osteoarthritic cartilage tissue. COMP is present during earliest stages of human limb maturation, and is later found in regions where the joints develop. In healthy and diseased cartilage tissue, COMP is secreted by the chondrocytes

and is often associated with the collagen fibers. In late stages of osteoarthritis, a five--fold higher amount of COMP mRNA is produced by chondrocytes found in an area adjacent to the main defect in comparison to an area with a macroscopically intact appearance. The results indicate that COMP is involved in human limb development, is up-regulated in osteoarthritis and, due to its broad binding repertoire, COMP could play a role in the pathogenesis of osteoarthritis as a factor secreted by chondrocytes to ameliorate the matrix breakdown.

## OA CARTILAGE EXPRESS HIGHER LEVELS OF C-JUN PROTEIN, IL-1 ALPHA AND TNF- ALPHA THAN NORMAL CARTILAGE

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Objective: Investigation the occurrence of apoptosis, c-jun protein and most abundant cytokines in cartilage degradation and cell death TNF alpha (TNF) and IL-1 alpha (IL-1) in OA synovial membranes (SM) and cartilages and its comparison with controls. Material and methods: SM and cartilages from 20 patients with OA and 5 controls were used. Levels of IL-1 and TNF in tissue extracts were established immunochemically. The occurrence of cell death (active caspase – 3) and of c-jun protein was established in paraffin embedded cartilage and SM samples by immunohistochemistry. Results and conclusion: The expression of c-jun protein was observed in OA cartilage, but not in control cartilage, OA and control synovial membrane. We observed higher occurrence of cleaved caspase-3 in OA cartilage — 10 % of positive cells, than in OA synovial membrane, control synovial membrane and control cartilage. Furthermore, there was significantly higher expression of TNF in OA synovial membrane and cartilage than in control tissues although the expression of IL-1 was significantly higher only in OA cartilage, when compared to control tissues. We suggest, that increased occurrence of c-jun in OA cartilage might be consequence of our results, although no information about the activity of this protein is known. This work was supported by MH, CZ, grant No. NR/7907-3

## INFLUENCE OF GLYCOXIDATION PROCESSES ON PENTOSIDINE ACCUMULATION IN ARTHRITIS AND DIABETES MELLITUS

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Introduction: Pentosidine (PEN), non--enzymatic cross-link of proteins, represents Advanced Glycation End-products (AGEs) and is considered as indicator of pathological changes of connective tissues caused by specific disorders in metabolism of proteins, fats and carbohydrates. Aims: In this study we focused on determination of pentosidine in patients with diabetes mellitus (DM) and chronic arthritis as the most serious states associated with PEN accumulation in the organism. Our next approach was PEN determination in biological samples from C57/6 black mice with spontaneously induced arthritis and testing the effect of vitamin C and Boswellin supplementation to inhibition of PEN formation in vivo. Methods: For PEN determination we established sensitive reverse phase

HPLC method with fluorescent detection which was applied to serum and urine samples of patients with osteoarthritis (OA), rheumatoid arthritis (RA), diabetics of type 1 and 2 and healthy controls. Results and conclusions: In active RA and DM2 patients we found approximately two times higher PEN than in healthy controls, but also in OA, elevation of PEN was observed. Our results have shown that pentosidine plays important role in pathogenesis of chronic joint diseases and DM complications, especially those associated with glycoxidation, systemic inflammation and oxidative stress. Supported by Ministry of Health of Czech Republic (grant No.NR/7895-3 and research project No.00023728)

## A SENSITIVE CE METHOD FOR DETERMINATION OF ENDOGENOUS CHONDROITIN SULFATE IN BLOOD SERUM

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Qualitative and quantitative determination of serum chondroitin sulfate (CS) is very important as information could be received in respect to structural alterations of serum CS in several pathological conditions along with its pharmacological profile. However, the structure of serum CS and the factors influencing its structure and concentration have not yet been fully identified. This is due to the low blood concentration of CS and a general lack of adequate analytical methodology that ensures high recovery of CS and sensitive determination. The aim of this study was to develop a serum pretreatment procedure and an accurate analytical methodology for the determination of the CS disaccharide composition. Serum samples were treated with non-specific protease to degrade serum proteins. CS chains were then recovered by precipitation and following treatment with chondroitinases ABC and AC II, the composition of disaccharides was determined by reversed phase capillary electrophoresis and UV detection at 232 nm. Serum was found to be rich in 4-sulfated and non-sulfated CS derived disaccharides. Application of the proposed method in serum spiked samples with CSs from various sources showed that it can also be applied for the quantitative analysis of total CS content as the sum of individual constituent disaccharides.

## REDUCED BONE STRENGTH AND COLLAGEN ORGANIZATION IN FEMALE MICE WITH DELETION MUTATION IN COL2AL GENE

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Mutations in COL2A1 gene coding for type II collagen have been shown to cause chondrodysplasia and osteoarthrosis. Transgenic Dell(+/-) female mice carrying a 150 bp deletion mutation in Collal gene are also known to suffer from progressive osteoarthrosis. Since endochondral ossification of cartilage models is involved in long bone development we investigated in this study whether changes in the properties of bone and spine would be manifested

in Dell(+/-) transgenic female mice. The mean size, morphology, breaking strength, stiffness, and mineral content of the femurs of female control and Dell(+/-) mice were measured, and distal femurs were immunostained for type II collagen. The samples from femoral and vertebral bone, and annulus fibrosus of the intervertebral disc were examined using polarized light microscopy. In addition, hydroxypraline and calcium contents were determined from the humeri. The breaking force of femoral bone was 24 % (p=0.01) lower in the transgenic mice in comparison with the controls, despite the fact that femoral size, morphology and mineral density of the 15--month-old transgenic mice were the same as in the controls. No differences in hydroxyproline or calcium content, or dry mass of the humeri could be observed between the groups. In polarized light microscopic analysis, the parallelism of the femoral bone collagen network was 4% lower (p=0.017) in the transgenic mice. Also in the vertebral bone, the birefringence was 27 % (p=0.01), and in the annulus fibrosus of the intervertebral disc 41 % (p=0.006) lower in the transgenic female mice (15 to 21-month-old) than in the age-matched controls. Femoral cortical bone had islets positive for type II collagen both in the control and transgenic mice. In conclusion, Del 1 (+/-) mice have decreased collagen fibril organization, possibly explaining the observed lower bone breaking strength. The deletion mutation in Col2al gene changes the biomechanical properties of murine cortical bone.

## LYSYL HYDROXYLASE 3 (LH3) CATALYZED GLYCOSYLATION IS ESSENTIAL FOR BASEMENT MEMBRANES

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Lysyl hydroxylase 3 (LH3) is a multifunctional enzyme possessing lysyl hydroxylase (LH), galactosyltransferase (GT) and glucosyltransferase (GGT) activities in vitro, and thus being able to form hydroxylysine--lmked carbohydrate structures in collagenous proteins. In order to investigate the significance of these modifications, genetically manipulated LH3 mouse lines were generated. In these mouse lines LH3 gene was knocked out, the LH activity of LH3 was specifically inactivated (LH-mutant) and the mRNA level of LH-mutant was dramatically reduced. The analyses of mouse lines indicate that LH3 has LH and GGT activities in vivo and LH3 is the main molecule responsible for the GGT activity during early development. The lack of GGT activity of LH3 disturbs correct type IV collagen distribution thus disrupting the formation of BMs during embryogenesis leading to lethality at E9.5. The lack of LH activity of LH3 does not disturb the embryonic development, but the structure of BM and the collagen fibril organization were affected in the newborn skin and lung lacking the LH activity of LH3. Together these findings indicate that the multifunctional LH3 is required for formation of normal BM and furthermore, GGT activity, not the LH activity of LH3, plays a key role in the

formation of BM and thus is indispensable for mouse embryonic development.

## CHONDROGENIC PROGENITOR CELLS DERIVED FROM LATE STAGES OF HUMAN OSTEOARTHRITIS

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Osteoarthritis (OA) is expected to become the fourth leading cause of disability by the year 2020. As a hallmark of late-stage OA, in addition to diseased chondrocytes, fibroblast-like chondrocytes emerge. With the help of cell culture, in situ-hybridization, immunohistochemistry, Western blot, real-time RT-PCR and microarray we have characterized the two cell types from human OA tissue in vivo and in vitro to judge their chondrogenic potential. Both cell types show de-differentiation on a plastic dish with high COMP and low sox-9 amounts, similar to fibroblasts. In 3D alginate culture, diseased chondrocytes exhibit a newly emerging collagen type II expression, as well as increased amounts of sox-9. However, they are not able to stop their collagen type I expression. In contrast, fibroblast-like chondrocytes decrease their COMP and collagen type I synthesis, but increase their sox-9 and collagen type II expression. Also found in OA cartilage are progenitor cells with unregulated PTHrP receptor, upregulated RANTES and ADAMTS5. These cells can be differentiated into osteoblasts, adipocytes and chondrocytes. Even without any pathological OA influences in 3D culture the diseased chondrocytes cannot re-differentiate beyond their in vivo status. The re-differentiation efforts of the fibroblast-like chondrocytes lead to a more chondrogenic expression pattern compared to their in vivo status. This shows a more flexible adaptation to changing environmental conditions and, therefore, they act more like progenitor cells than diseased chondrocytes.

## SYNTHETIC ELASTIN: MOLECULAR AND CELLULAR INTERACTIONS

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An essential step in elastin formation requires the rapid association of tropoelastin molecules. Using surface plasmon resonance, we find that tropoelastin tightly binds its tropoelastin partner. This interaction is strengthened by the exposure of extremely strong, cryptic interaction sites in the amino- and carboxy-terminal regions of tropoelastin. Full-length tropoelastin bind with picomolar dissociation constants to two fragments of tropoelastin, one fragment spanning from the ammo-terminus to domain 18 and the other fragment from domain 27 to the carboxy-terminus. These fragments independently demonstrate strong heterodimerization. Strong binding culminates in the formation of a droplet-like solid mass of tropoelastin. Light scattering and microscope measurements reveal these spherical droplets are several microns across. Lysine-reacting chemical and enzyme-assisted cross-linking conditions give cross-linked products, demonstrating that the droplets have multiple exposed lysines on their surfaces and culminate in dense clusters of aggregated droplets and synthetic elastin fibers. Three-dimensional culturing demonstrates elastic synthetic matrix interactions coupled with coordinated matrix remodelling.

## MICROBEADS COATED BY DE NOVO SYNTHESIZED TISSUE AS A SYSTEM FOR TISSUE DELIVERY

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Recently, the field of tissue engineering has rapidly progressed, but often the conventional scaffold approach presents some limitations in the realization of viable thick tissues. One of the most important problem is the non adequate transport properties throughout the scaffold inducing hypoxia, nutrient insufficiency, and waste accumulation that in many cases determine the formation of necrotic areas in the inner sections of the resulting constructs.

Therefore, new technologies for fabricating functional thick tissue with well--organized structure are required. Okano et al. has recently exploited an original method of tissue engineering, starting from monolayer cell cultures to create a three--dimensional structures via the layering of individual cell sheets, thus either modulating scaffold thickness and overcoming problems connected with inadequate nutrients and metabolic traffic within the constructs synthesized.

In this work we report the development of a new approach that combines at the same time both the normal scaffold method and the new strategy proposed by Okano. In this case, instead of starting from single cell sheets, we decided to use single gelatine cell-seeded microcarrier to support a 3D new bio-hybrid formation. In fact, by microbeads multi-aggregation, it is possible to assembly a single construct characterized by a uniform cellular colonization and a functional tissue formation throughout its thickness. Furthermore, our results show that such system allows overcoming any shape limitations represented by the traditional pre-defined scaffold design approach, indicating microbeads as a valid alternative to the production of thick, viable tissue, and thus revealing a possible solution for the clinical repair of several damaged tissue.

## OSTEOCLASTIC ACTIVITY IS POSITIVELY CORRELATED WITH SERUM HYALURONAN IN BREAST BONE METASTASIS

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Metastatic spread to bone is frequent in advanced breast cancer. Bone-specific alkaline phosphatase (BAP) for bone formation and the N-telopeptide of type I collagen (NTx) for bone resorption have been developed for assessing bone disease. Hyaluronic acid (HA) plays an important role in activation and function of osteoclasts. Zoledronic acid (ZA), a bisphosphonic compound, is used for reducing skeletal complications. We investigated the correlation between HA and bone metabolic process. Serum samples were collected from 21 breast cancer patients with bone metastases. Analyses were performed by ELISA for NTx and BAP and by enzyme-linked binding protein assay for HA at baseline and after 2 monthly doses

of 4 mg ZA. At baseline, HA, NTx and BAP were elevated in breast cancer patients as compared to healthy individuals. In follow--up, HA and BAP showed relatively decreased levels, while NTx showed excellent response to ZA administration (32.3 % and 50.5 % decrease, p<001). Correlation showed that HA was positively correlated with NTx (r=0.473, p=0.0063) and not with BAP (r=0.129, p=0.4816), concluded that HA is involved in bone resorption since osteoclasts have been shown to possess HA-binding surface proteins (CD44). Furthermore, a vicious cycle of HA in bone resorption is suggested: an increase of HA enhances the adhesion and activation of osteoclasts on bone surface and. there is a feedback of circulating HA since bone extracellular matrix is degraded and HA is released again in circulation. Acknowledgements: This work is financially supported by the Hellenic General Secretary of Research & Technology (program PENED2003, code 03ED970).

## MICROFIBRILS, ELASTIN FIBERS AND COLLAGEN IN HUMAN AND BOVINE INTERVERTEBRAL DISCS (IVD)

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Microfibrils have been revealed by immuno fluorescent staining of fibrillin-1 in young (12–17 yrs) normal human lumbar IVD and bovine tail discs, and their localisation compared to that of elastin and collagen fibres. The organisation of microfibrils in bovine tail discs was found very similar to that seen in the human discs; however there was a striking difference between the network seen in the outer annulus (OA) and in the nucleus pulposus. In OA region, abundant microfibrils predominately organised in the inter-territorial matrix. Within each lamella they appeared to be oriented parallel to each other and mainly co-localised with elastin fibres. The elastic fibre network (microfibrils plus elastin fibres) was aligned in the same direction as collagen bundles, suggesting a close relationship here between the elastic network and the primary structure of collagen network. Microfibrils were also densely localised in the inter-lamellar space and formed bridges crossing individual lamellae. In the inner annulus, the organisation of microfibrils was altered; microfibrils were filamentous and distributed not only in ECM but also around the cells and co-localised with elastin less than in the outer region. In the nucleus pulposus, fine microfibrils were densely distributed around cells where elastin was not detected; however elastin was found mainly present in the inter-territorial matrix. Thus there is a different distribution of microfibrils in the different regions of the disc, possible reflecting different functions. They may play a more mechanical role in outer annulus and a more biological role in the nucleus.

## COLLAGEN PEPTIDES ACT AS NUTRACEUTICALS

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**Background:** Peroral administration of bovine skin hydrolysate is used succesfully as nutraceuticum mainly in patients with osteoarthritis. Unfortunately the mode of action is unknown. **Methods:** Antibodies directed to the rat collagen hydrolysate which is used as nutraceuticum were prepared by immunization of sheep and afterwards purified using CNBr-activated Sepharose 4B. Prepared antibodies were used for immunofluorescent and immuno--gold electron microscopic detection in tissues of mice fed with collagen hydrolysate. **Results:** Positive immunofluorescence was observed in the cytoplasm of hepatocytes and chondrocytes as well as in the fibrillar components of extracellular matrix. Positive signals were found also in other organs as in oesophagus, kidneys, spleen and sternum. The electron microscopic evaluation confirmed a presence of antigenic determinants of the rat collagen hydrolysate in mice tissues and organs using immuno-gold technique. Conclusions: The authors anticipate that these findings may help to elucidate the mode of action of collagen hydrolysate in diseased human beings. Supported by Ministry of Health of the Czech Republic (research project No. 00023728)

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The journal Locomotor System will publish the papers from the field of locomotor apparatus of man which are above all concerned with the function, physiological and pathological state of the skeletal and muscular system on all levels of knowledge, diagnostical methods, orthopaedic and traumatological problems, rehabilitation as well as the medical treatment and preventive care of skeletal diseases. The object of interest are interdisciplinary papers of paediatric orthopaedics and osteology, further object of interest are problems of biomechanics, pathobiomechanics and biorheology. The journal will accept the original papers of high professional level which were not published elsewhere with exception of those which appeared in an abbreviated form.

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Pokroky ve výzkumu, diagnostice a terapii

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**Chairmen:** PETRTÝL M., MARCZYŃSKI W.



Lectures in English, in Czech anf/or Polish 20 minutes with discussion,
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**PERSPECTIVE ARTICLE**

# THE VALUE OF SURGICAL RELEASE OF THE ILIOTIBIAL BAND IN TREATMENT OF IDIOPATHIC VALGUS DEFORMITY OF THE KNEE JOINT AND IN HABITUAL PATELLA SUBLUXATION IN CHILDREN AND ADOLESCENTS

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**Key words:** Knee valgus, patella subluxation, iliotibial band, hyperpressure of the patella sundrom

## Summary

In the years 2000–2004 in Paediatric Orthopedic and Rehabilitation Department of Medical University of Lublin were performed surgical iliotibial band release in 70 children as treatment of valgus of the knee (40 patients), valgus of the knee with subluxation of the patella in extension of the knee (18 patients), valgus of the knee with hyperpressure of patella syndrome (11 patients) and in one case knee valgus after inflammatory in newborn period. The authors found that surgical release of iliotibial band is an easy and effective method of treatment of knee valgus, in patella subluxation and in hyperpressure syndrome of the patella.

## Introduction

The knee joint is not only the biggest joint of human body, but also it is the most sensitive joint and gets injured easily (**1, 6, 7, 9, 13**).

The habitual and recurent dislocation of the knee cap (patella) causes serious weakness of the joints in consequence leading to the necessity of surgical treatment.

While the surgical reconstruction of the knee cap and thigh it has been noticed that the iliotibial band (tractus iliotibialis) is tense (**Fig. 1**) (**2, 6, 7, 11, 15, 17, 21**).

It could even lead to the transposition of the tibia and fibula to the lateral side.

Intraoperative observations have proved that iliotibial band apart form the main part is also going towards the patella and to the patella tendon (**Fig. 2**) (**3, 14, 15, 19**).

This factor is very important both in the etiopathology of the patella luxation, subluxation, in valgus of the knee and in the "hyperpressure syndrome of the patella". Similar observations have been

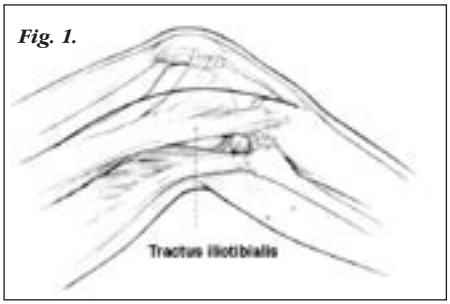

*Fig. 1.*


*Fig. 2.*

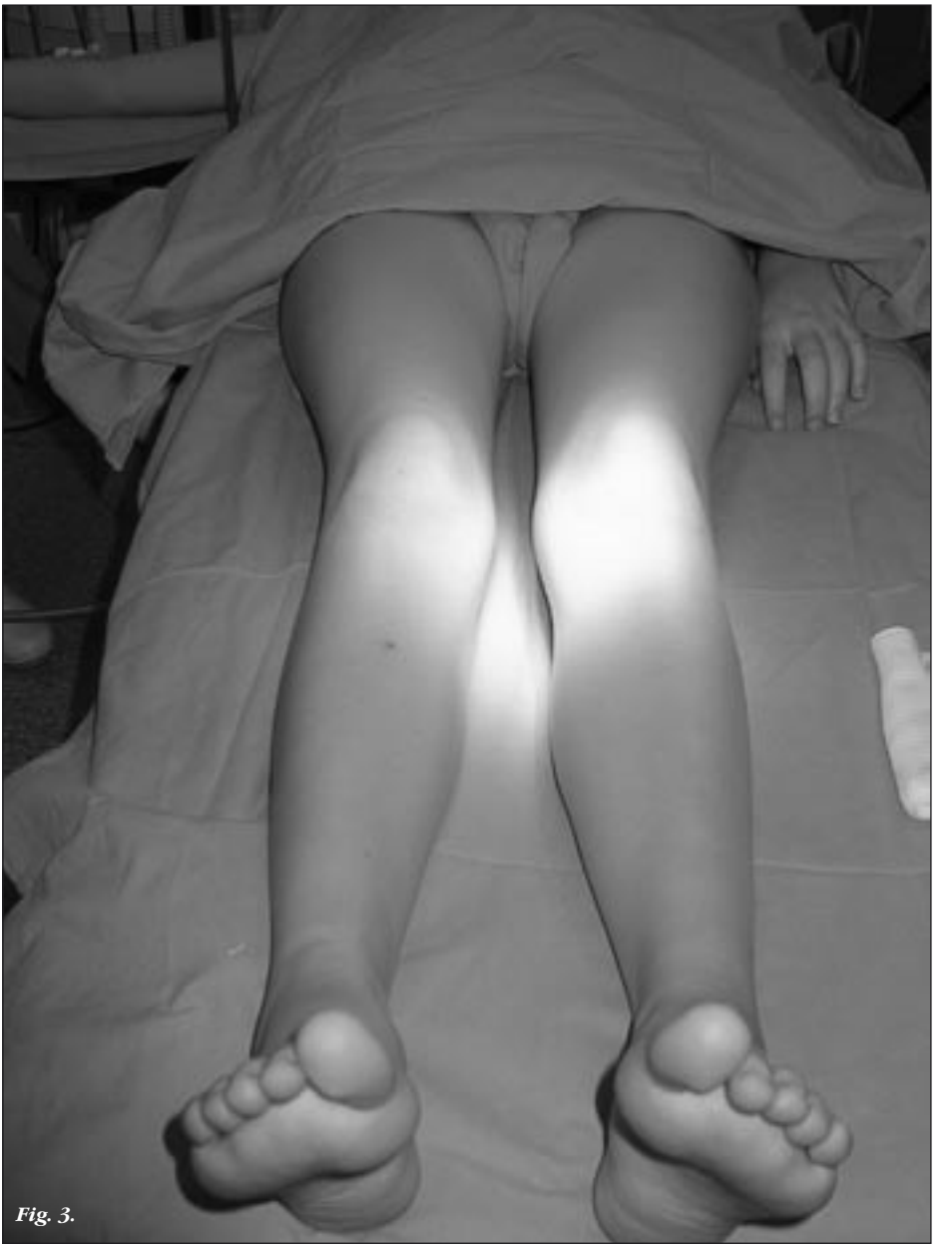

*Fig. 3.*

*Fig. 4.*

found in literature (**5, 8, 10, 11,12, 14, 15, 16, 18, 19, 20**).

## Material and Method

In years 2000–2004 we have performed surgical iliotibial band release in 70 children, 27 boys and 43 girls. The age of surgery was from 10 to 22 years (average 13,7) at girls and from 4 to 19 years (average 12,4) at boys.

In 19 children the contracture of the iliotibial band was on one-sided (8 times on right leg, 11 on left leg), in 51 children the contracture was both-sided. All together it was 121 legs treated by this method.

Patients were devided into groups of various pre-operative symptoms:

- valgus of the knee – 40 patients (22 girls, 18 boys) (74 legs)
- valgus of the knee with subluxation of the patella in extension of the knee – 18 (10 girls, 8 boys) (31 legs)
- valgus of the knee with hyperpressure of patella syndrome – 11 (11 girls, no boys) (15 legs)
- pathological (after inflammatory in newborn period) knee valgity 1 (1 girl, no boys) (1 leg)

In all cases we performed the surgical release of the iliotibial band. The incision was 5–10 cm over the joint space on the lateral side of the thigh. The fasciotomy of the fascia lata and tractus iliotibialis we make in "Z" shape. During operation we

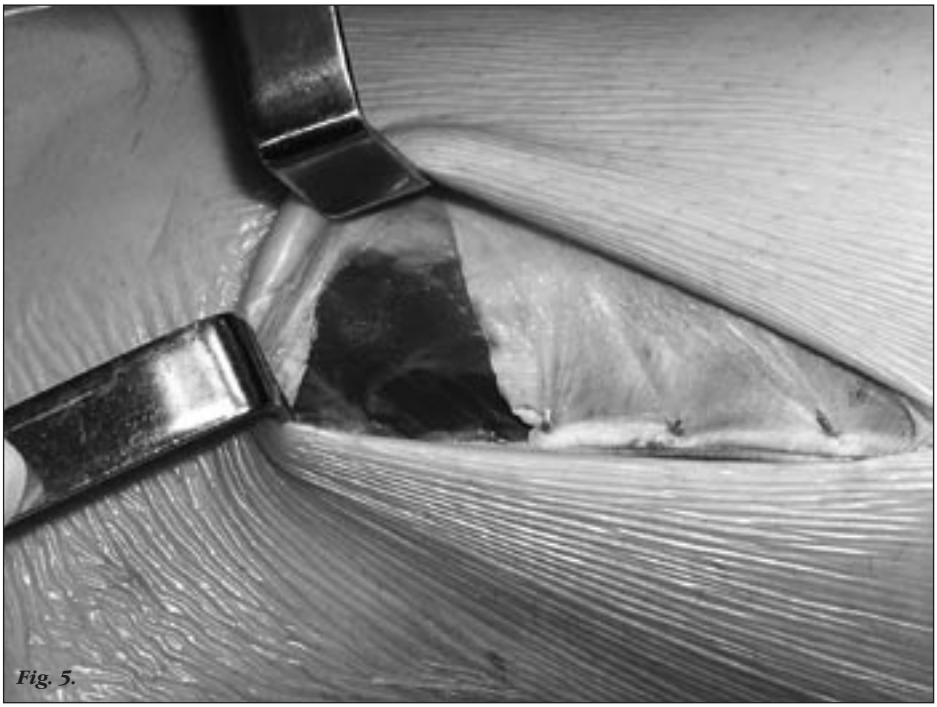

*Fig. 5.*

temporary flexed and extended the knee to make sure that all fibers are released (**Fig 3, Fig 4, Fig 5**).

## Results

We have performed follow up examinations (3–36 month postoperatively) in 45 patients (77 legs).

We estimated: 27 patients from the group of valgus deformity of the knee, 14 patients from the group of valgus of the knee with subluxation of the patella, 3 patients from the group of valgus of the knee with hyperpressure of patella syndrome, 1 patient from the group of the pathological knee valgity

The valgus angle preoperatively reached 12 to 35 – on average 16 for the right leg and 16,5 for the left. Postoperatively the axis of the knee improved in all patients and was from 5 to 20 degrees – on average 8,4 for right leg and 8,3 for left (**Fig 6, Fig 7**).

In patients with patella subluxation we have examined 23 legs. In 11 patents (18 legs) the axis of the knee improved. The remaining 3 patients (5 legs) later have been qualified for the complete reconstruction of patello-femoral joint with patella tendon transposition. In patient with post inflammatory deformation the angle has improved from 15 to 7 degree, but after the following 34 months reached another 20 degrees and patients had the osteotomy of the femur.

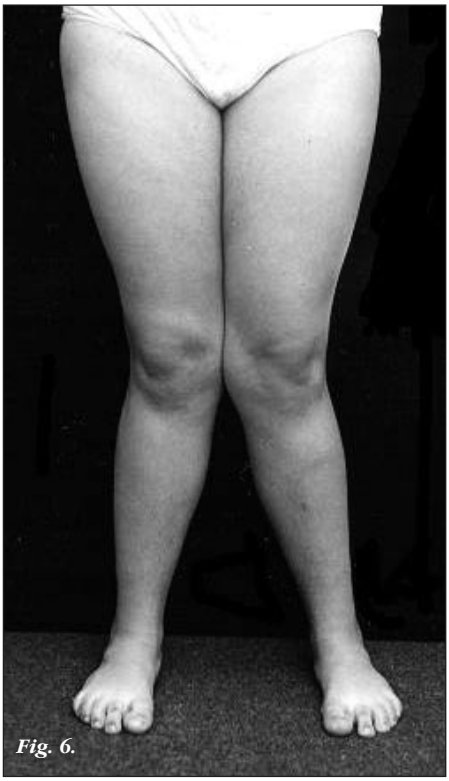

*Fig. 6.*

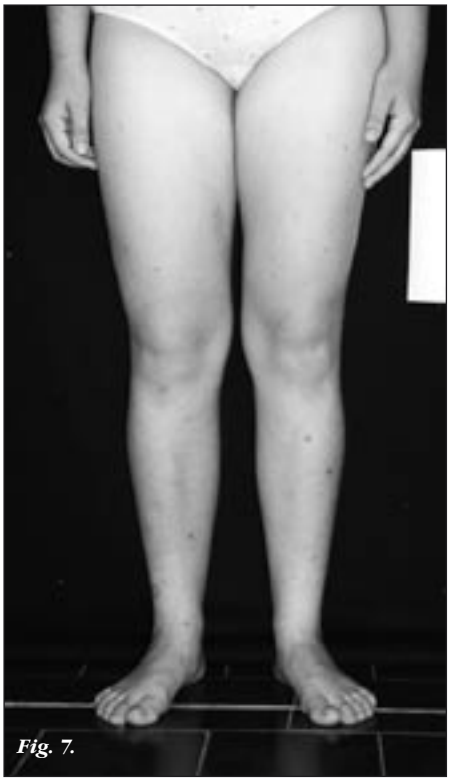

*Fig. 7.*

## Conclusions

1. The valgus of the knee, valgus of the knee with subluxation of the patella, valgus of the knee with hyperpressure of patella syndrome are related with the contracture of the iliotibial band
2. The iliotibial band release shows good results in the correction of the axis of the knee.
3. In the patients with knee valgus with hyperpressure syndrome of the patella, clinical symptoms disappearance, the passive shift movement of the patella towards medial side of the knee is possible.
4. In the group of subluxation of the patella with knee valgus the effectiveness of this method is 78%.
5. The surgical release of iliotibial band is an easy and effective method of knee valgus correction in idiopathic valgus of the knee, in patella subluxation and in hyperpressure syndrome of the patella.

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**ORIGINAL PAPER**

## BIOMECHANICAL EFFECTS CREATE THE SHAPE AND VOLUME OF OSTEOARTHRITIC DEFECTS IN SUBCHONDRAL BONE

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### Summary

Biomechanical loads and resulting biochemical processes are the basic supports of tissue existence. The spherical stress tensor regulates the intensity of metabolical processes (the rate/speed), the deviator stress tensor initiates („starts“) the metabolic processes. The bone tissue is very sensitive on the shear stresses. In the parts of bone tissue where the bone remodeling equilibrium has been broken, i.e. where the upper „permissible“ limit of bone dynamic stability has been exceeded, the bone is pathologically reconstructed. Bone defects described (for example) by radiologists as cysts have the shape predetermined (and limited) by the certain fields of shear stress. The regions (like cysts) are often spherical, sometimes bulbous or pear-shaped. These shapes are completely identical with the shapes (or lines in a plane) of izochromats. These regions – the pseudocysts - are filled with granulations containing inflammatory, spindle shaped elements, multinuclear cells and the collagen of the III$^{rd}$ type.

**Keywords:** biomechanics, biochemics, osteoarthritis, granulations, shear stress, photostress, isochromatic lines, cytokines, metaloproteinases, pyridinolins, collagen, shear stresse

### Souhrn

Zánětlivé procesy v subchondrální kosti kloubů patří mezi velmi častá onemocnění. Změny napjatosti v chrupavce a v subchondrální kosti významně ovlivňují metabolické rekonstrukční procesy ve tkáních a kvalitu extracelulárního materiálu. Buňky mají schopnost ve svém okolí synthetisovat funkční matrici. Primárně jsou m.j. ovlivňovány mechanickými účinky – **smykovým napětím,** které iniciuje („startuje“) vznik signálních molekul, na příklad oxidu dusíku. Tyto molekuly přispívají k akceleraci nebo k retardaci následných metabolických procesů v kosti. Biomechanické a biochemické signály aktivizují procesy rekonstrukce tkáně, a to

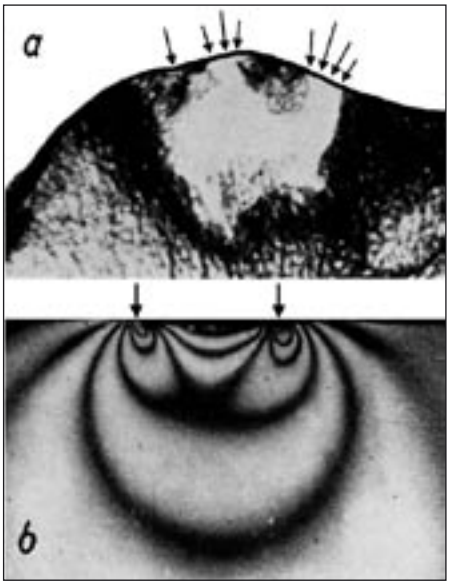


**Fig. 1.**
a. Two interconnected regions of subchondral bone by the pseudocysts;
b. Izochromatic curves of the 3rd order predetermined the fields of pseudocysts, (2)

jak procesy její remodelace (u fyziologicky normální tkáně), tak procesy patologické (u degenerující tkáně). Velká lokální zatížení vedou k narušení spojitosti chrupavky (k separaci kolagenu II. typu, proteoglykanů a dalších strukturálních komponent chrupavky) a k patologickým přeměnám. Zatížení se poté koncentruje do malé lokality subchondrální kosti, kde dochází k velkým perturbacím napětí. Extrémy („špičky“) napětí jsou v korelaci s intenzitou často až nesnesitelných bolestí. Degenerativní strukturální změny v subchondrální kosti mají v příčném řezu oválný, kruhový až hruškovitý tvar. Tyto tvary jsou identické s liniemi izochromat, tj. křivek konstantních rozdílů hlavních napětí. Jen jistý řád

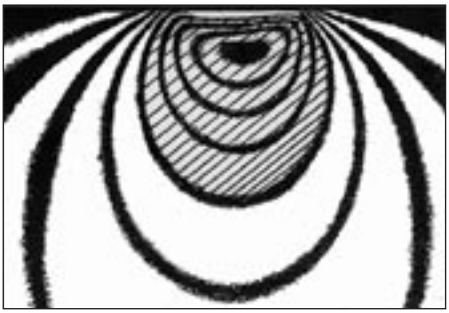

**Fig. 2.** The izochromats lines of constant shear stresses in subchondral bone. The cross-hatch area predefine the volume of tissue degradation and creation of granulations.

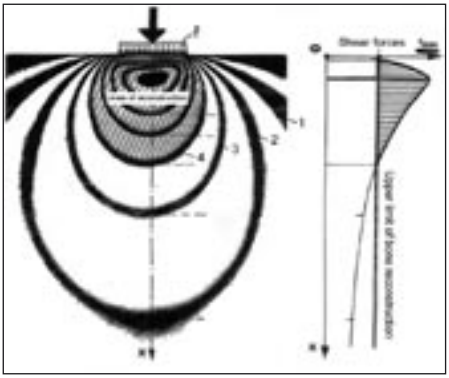

**Fig. 3.** Izochromats of the 4th order and higher orders (the hatch area) determine the space of tissue granulations

izochromat omezuje prostor probíhajících degenerativních změn. Tento prostor je někdy na rentgenovém snímku popisován jako cysta. Ve většině případů se jedná o pseudocysty, oblasti degenerované tkáně vyplněné granulačním materiálem, vesměs s převládajícím kolagenem III. typu, proinflamatorními cytokiny a enzymy štěpícími protejny.

**Klíčová slova:** biomechanika, biochemie, osteoarthritis, granulační tkáň, izochromaty, colagen, enzymy, pyridinolin, smyková napětí

## Introduction

Osteoartrhritis (OA) is mostly thought to be of degenerative pathology. This is true in early OA stage only when solely avascular cartilage is injured and therefore no inflammation may take place. On the other hand some constituents of joint compartment (synovialis, subchondral bone, periarticular soft tissue) are inflamed. Radiologists use to describe bone defects in subchondral bone mostly as cysts. However according to pathological definition cysts are inborn empty holes surrounded inside by epithelium.

Collagen type III which was earlier found by Adam et al. (**7**) in bone tissue injured by OA is namely present in young and newly formed tissues but not in bones. Therefore we have decided to verify this finding by histology and as well as by proinflammatory cytokines and metaloproteinases in holes fulfilled with granulations. The biochemical changes are initiated by biomechanical inducement also.

The bone tissue is very sensitive on the shear stresses (**1**), (**3**). In the parts of bone tissue where the bone remodeling equilibrium has been broken, i.e. where the upper „permissible" limit of bone dynamic stability has been exceeded, the bone is reconstructed and (for example) in the case of subchondral bone is formatted into the *granulate structure*. The region of granulation formation is usually very distinct. Regions of structural changes are identified by sensors of cells that are sensitive to shear flows of liquids in the extracellular matrix. Limited levels of shear flows in disordered regions are in plane projections identical with isochromats, i.e. with the curves (in a plane) of constant shear stresses $\tau_i = (\sigma_1-\sigma_2)/2$. Bone defects described (for example) by radiologists as *cysts* have the shape predetermined (and limited) by the certain fields of shear stress. The regions (like cysts) are often spherical, sometimes bulbous or pear-shaped.

## The range of degenerative areas in subchondral bone

The regions of degenerative tissue changes are predetermined by the physiological inadmissible levels of shear stresses. The cells of subchondral bone response to excess of shear stresses by the production of signal molecules (**4**), (**5**). These molecules start up the degenerative metabolism processes. The areas of disturbances are bordered by the izochromatic curves (**Fig. 1**).

These shapes of pseudocysts are completely identical with the shapes (or lines in a plane) of *izochromats* that can be defined also as the curves with constant differences of principal stresses, i.e. $(\sigma_1 - \sigma_2)$. The granulation filling holes (like cysts/pseudocysts) contain the high concentrations of metalloproteinases and proinflammatory cytokines. These regions are filled with granulations containing inflammatory, spindle shaped elements, multinuclear cells and the collagen of type III.

The visual example showing the shape and extent of pseudocysts in subchondral bone is obvious from **Fig. 2** and **Fig. 3.** The izochromats are more dense under the load. The cross-hatched areas predetermine the range of tissue granulations. The shape of pseudocysts is identical with the course of

| Bone form of OA | | | |
|---|---|---|---|
| TEP joint | n | age | F/M |
| knee | 35 | 70.2 ± 5.6 | 28/7 |
| hip | 45 | 64.5 ± 11.1 | 34/11 |
| total | 80 | 67.5 ± 9.5 | 62/18 |

**Tab. 1.** Characteristics of the group of OA patiens (F-female; M-male)

limiting izochromatic curve. The hatched area shows the space where the bone remodeling equilibrium has been interruptioned. The limiting shear stresses overrun the ultimate stresses $\tau_{ult} = (\sigma_1 - \sigma_2)/2$, where $\sigma_1$ and $\sigma_2$ are the principal stresses.

## Clinical verifications

OA joint compartments of 80 patients obtained during surgery (45 hips and 35 knees) were subjected for investigation – X-ray, histology and biochemical examinations: granulations, synovialis, cartilage, synovial fluid. Control tests were performed in samples from unaffected joint (trafic accident) received from Dept. Forensic Med., 1st Med.Fac. Charles Univ. Prague. Control sera were taken from 23 healthy volunteers.

The **defects of subchondral bone in OA** are filled with *soft tissue containing inflammatory and spindle shaped elements*. Interestingly, the soft tissue filing the malformations contains co llagen III, which is not commonly found in bone tissue. In addition, the defects contain tissue showing *strong inflammatory processes followed by higher production of cytokines and metalloproteinases*.

Pathological definition indicates that *cysts are holes surrounded by epithelium* (**6**). Whereas in OA, according to our histological findings no holes in subchondral bone are present. The cytological appearance of the soft tissue inside the defects is typical for the *chronic granulomas of inflammatory origin*. Such granulomas represent the reactive process in a wide scale of stimuli similarly as foreign bodies, some bacterial, viral and/or parasitic infections.

Moreover, in extracts from granulation tissues metalloproteinases MMP-2, MMP-3 and MMP-9 were up regulated when compared to extracts from subchondral bones obtained from healthy controls. Furthermore, the proinflammatory cytokines such as IL-1β, IL-8, IL-10 and TNF-α were in granulation tissues increased when compared to healthy controls as well (**Tab. 2.**).

The *multinucleate giant cells formed by fusion of macrophages represent the most prominent feature of these processes* (**15, 16, 17, 18**). The macrophage fusion is stimulated by interleukins such as IL-4 and IL-13 (**14**).

Furthermore, the results obtained in analysis of biochemical markers are in line with data of *Anderson-MacKenzie* (**10**), suggesting that bone remodeling is fundamental even during the very earliest development of OA and occurs prior to detectable changes of cartilage or changes of the bone density.

| | TNF-α | IL-8 | IL-10 | IL-1α |
|---|---|---|---|---|
| Granulation tissues (ng/g DM) OA patients (n=80) | 2.62±3.94 | 8.11±20.04 | 1.24±3.52 | 0.24±0.21 |
| Bone (ng/g DM) healthy controls (n=3) | 0.38±0.01 | 1.22±1.11 | 0.23±0.05 | 0.05±0.01 |

**Tab. 2** Levels of cytokines in granulation tissues compared to healthy controls

By most authors it is thought that both IL-1 and TNF-α contribute independently to articular degradation. Furthermore, these cytokines may stimulate they own production and induce production of other cytokines such as IL-6 and LIF (leukocyte inhibitory factor) (**12**). In addition, the mentioned cytokines have an inhibitory effect on the connective tissue turnover (**13**).

Furthermore, IL-1 is direct activator of bone resorption involved to the destruction of bone and OA progression (**14**). Therefore, due to higher production of inflammatory cytokines and metalloproteinases, we suggest that *subchondral bone is involved to the process of cartilage degradation.*

To sum up, the *devitalised bone trabecules and pieces of devitalised cartilage observed in bone defects can be inductors of granuloma formation.* In line with this hypothesis are findings from Glowacki et al. 1989 that the particles of devitalised bone subcutaneously implanted into the rat induced formation of multinucleate giant cells similar to osteoclast (**20**). It is necessary to mention that *both types of multinucleate cells, i.e. osteoclasts and foreign body giant multinucleate cells represent the terminal step of the differentiation of cells of macrophage lineage* (**21, 22**). The histological inspection *suggests a role of these granulomas in the process of formation of bone defects.* Finally, the OA subchondral bone contains granulations which in X-ray resemble cysts. *Presence of collagen III and of proinflammatory cytokines verifies inflammatory origin of granulations.* The regulation of metalloproteinases is in agreement with those findings as well.

## Conclusions

1. The shape and the volume of degenerative reconstruction processes in subchondral bone are predetermined by the **limited level of shear stresses.**
2. **The bone equilibrium (the steady state) is disturbed when the limited level of shear stresses (in the bone element unit – BEU) is overpassed.** Then the subchondral bone is transmuted pathologically.
3. The formations of **pseudocysts were found in OA spaces.** They were fulfilled by tissue **typical for granulomas of inflammatory origin.**
4. **Round shaped defects were clearly visible in granulations.** OA defects are without any epithelium on the border and are fulfilled with soft tissue containing inflammatory and spindle shaped elements, most likely fibroblasts characteristic for granulations.
5. The **multinucleate giant cells** of Lnngerhans or foreign body type represented the prominent determinant of the soft tissue inside the bone defects. Pieces of the devitalized cartilage or bone were frequently present in that soft tissue.
6. Granulations fulfilling holes contained high concentrations of **metaloproteinases and proinflammatory cytokines.** Tissues of joints cought by OA showed according to biochemial tests an intensive turnover.
7. **Proinflammatory cytokines mainly Il-1, Il-8 and TNF-α were increased in synovial fluid** as well as in synovialis, cartilage and granulations., that play a pivotal role in OA development, i.e. in cartilage and bone

damage. The cytokines are inhibitors of connective tissue turnover.

8. Round shaped defects were clearly visible in X-ray pictures of investigated articular bones (**Fig. 4A**) and they correspond with distinct defects in macroscopic slices of the joint heads (**Fig. 4B**). **No epithelium on the border of the defects was observed.**
9. Moreover, the bone vitia were filled with **soft tissue containing inflammatory and spindle shaped elements, most likely fibroblasts.**
10. The multinucleate giant cells of Langerhans or foreign body type represented the prominent determinant of the soft tissue inside the bone malformations (**Fig. 4C**). Pieces of the devitalized cartilage or bone were frequently present in the soft tissue (**Fig 4D**). Interestingly, signs of the extensive bone remodeling were observed also in non-affected trabecular bone in the neighborhood of the defects (**Fig. 4E**). Furthermore, **collagen type III, typical for newly formed tissues but not for bone, was immunohistochemically detected in the soft tissue filling the bone malformations** (**Fig. 4F and Fig. 4F**).
11. Biochemical tests have shown **intensive turnover in articular tissues.** Urinary PYR and D-PYR and serum CHON served as indicators of the break down of joint components. In the tested group of bone form of OA were all these markers up regulated when compared to healthy controls . In addition, the marker of osteoblastic activity BAP was up regulated in serum as well.

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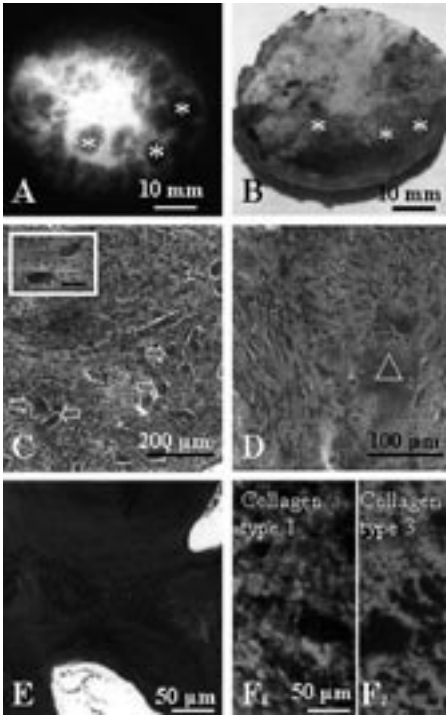


**Fig. 4.** Extirpated osteoarthritic head of human femur (Adam M., Pešáková V., Smetana K., Hulejová H.)
(**A**) X-ray photograph,
(**B**) macroscopic slice;
(**C, D, E**) histology of content of the defect and remodeling of the trabecular bone in the vicinity of defect (see the difference in the staining of bone trabecule, the light blue color indicates disruption of glycosaminoglycans of the extracelullar matrix).
(**F**) Immunohistochemical detection of collagen type 1 (**F1**) and type 3 (**F2**). The bone defects are marked with asterisks (*) and representative multinucleate giant cells with open arrows (⇒). The insert in Figure (**C**) demonstrates giant cells in higher magnification (bar respond to 200 mm). Piece of devitalized cartilage inside the granuloma is marked with triangle (Δ). Hematoxylin-eosin staining (**C**) and blue trichrome staining (**D, E**).

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**REVIEW ARTICLE**

# GROWTH ZONES OF LONG AND SHORT BONES IN CHILDREN; DIMENSIONAL SHAPE OF GROWTH PLATE OF PROXIMAL FEMUR AND ITS SIGNIFICANCE IN ETIOLOGY OF THE EPIPHYSEAL SLIPPING

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## Abstract

The paper underlines the importance of growth zones and their blood supply in children. It describes possible injury to growth zone and to blood vessels during operative procedures of child's foot. It points out importance of dimensional shaping of growth plate of proximal femur and its significance in etiology of slipped capital epiphysis.

**Key words:** growth zones of bones, blood supply, three dimensional (3-D) shape of growth plate of proximal femur

## Introduction

Well formed epiphysis with normal articular cartilage are necessary conditions of proper joint congruence and motion. The growth process of epiphysis of long bones in children happens due to activity of epiphyseal growth zones – basal layer of articular cartilage. The similar processes happen in short bones (metatarsal bones, wrist bones) which grow due to activity of basal layers of their articular cartilages.

Thus the activity of growth plate is necessary for proper ossification and increase of bone mass of metaphysis.

The blond supply of the growth plate comes both from epiphysis and from metaphysis. But the growth plate itself forms a barrier for blond vessels. Epiphyseal growth zone gets its blond supply only form epiphysis (**1–7**). Directly underneath the growth zones in children lie layers of immature bone tissue susceptible to mechanical stress (**8, 9**), (**Fig. 1**). Underneath the articular cartilage in adults lies compact

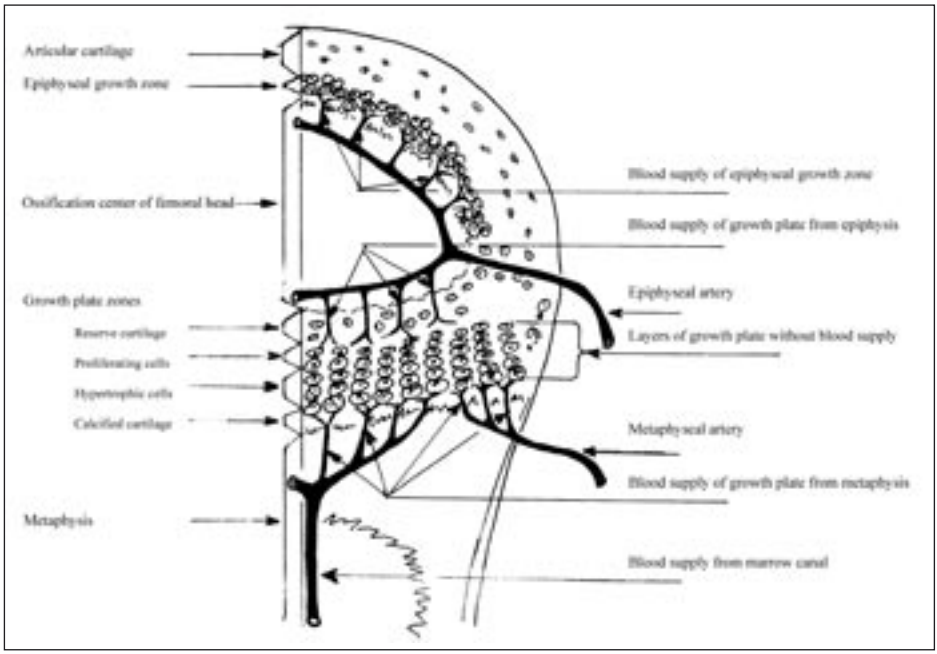


**Fig. 1.** Scheme of blood supply to the epiphyseal growth zone and growth plate of proximal femur. Epiphyseal growth zone is the most distant layer to which blood is supplied in the growing femoral head. Growth plate forms a barrier for blond vessels. Directly underneath the growth zones there are layers of immature bone tissue.

bone layer which strengthens its junction with spongy bone tissue (**10**).

The presence of growth zones of long and short bones in children has significant clinical value since many congenital and acquired deformities are related to disturbances of their function. These include inflammatory disturbances, injuries and congenital growth disturbances of growth zones (epiphysesal and metaphyseal dysplasias).

## Growth zones of metatarsal bones in children

The basal layer of articular cartilage of short bones forms the growth zone with its blood supply. The growth process in these bones should be taken in consideration during planning of operative procedures on these bones. In very young children operative procedures should not include cutting out these layers since that would effects the growth of the bone. The extraction of two adjacent layers of articular cartilage during arthrodesis would be equal to cutting out two growth zones and would limit growth of two bones. Instead of such

procedure it should be advised to cut out the "interior" of the spongy bone tissue. In metatarsals such procedure should be performed the talus or the cuboid during corrective procedures of severe varus deformity e.g. in spasticity. During osteotomy of the navicular with elongation or wedge resection of the cuboid it is important to mind the place of osteotomy which should be far from articular surfaces in order not to disturb blood supply of growth zones.

## Dimensional shape of growth plate of proximal femur and its significance in etiology of slipped capital epiphysis

The growth plate of proximal femur in children shows changeability of dimensional shape according to the age of child. The largest pleating is in age of 5–8 years and it is very specific. Apart from sinuous shape of the whole surface of growth plate there are numerous smaller immersions and eminences. The whole surface of the growth plate is thus larger than the actual diameter of femoral head. The type of pleating allows firm and efficient junction of femoral head and neck. The same phenomenon is known to carpenters while joining two layers of wood. The same pleating of growth plate is present at other long bone ends.

It is known that total epiphyseal slipping is rather observed in very young children (1–3 year of age) when the growth plates are thick and without pleating. In older (over 5 years) children the slipping of physis is usually accompanied with fracture of metaphysis or/and epiphysis.

After 10th year of life the growth plate of proximal femur in children gradually becomes more spherical and the lack of pleating (more regular shape) also enables occurrence of slipped capital epiphysis. The direction of slipping is dependable on the direction of reacting forces and "inconvenient mechanically" shaping of growth plate in children after 10th year of life. The femoral head is displaced backward and downward – which is caused by cutting forces reacting during the flexion of femur in the hip joint.

## Conclusions

1. The changes of dimensional shaping of epiphyseal growth zone from pleated to more spherical enables occurrence of slipped capital epiphysis in children above 10th year of life.
2. Each arthodesis procedure or osteotomy close to articular cartilage in young children should be well planed. Any damage to the growth plates of metatarsal bones may limit their further growth

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**ORIGINAL PAPER**

## COMPUTER AID TO CHILD SCOLIOSIS TREATMENT

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### Abstract

Orthopaedists in the Czech Republic use corrective braces of type Cheneau or Cerny for conservative treatment of non skeletal scoliosis. The brace has force effects on a child spine and if it is used for enough long time the spine defect is corrected. The brace is made individually for each patient in this way: first, the negative plaster form of a child trunk and then the positive plaster form are made. The positive plaster form is deepened in the places where brace has to push on the patient trunk. The laminate brace which is made according to this plaster form pushes the child trunk at the place where the form was deepened (like a tight shoe principle) and on an appositive side of brace is a hole for trunk displacement. The paper shows computer algorithm for solving of the stress state in vertebrae and inter-vertebrae discs and the spinal curve correction under brace force effects for a concrete child patient. The stress state at the spine and spine deformation correction are solved according to the beam (spine) theory. The algorithm solves the spine stress state and deformation under brace force effect for concrete patient. The algorithm searches the ideal trunk load the patient trunk from brace to be the best correction of his spine defect. The algorithm and parameters were verified with treatment courses. The trunk surface load was checked by sensor plates which were put into braces to measure the load values between the brace and the child trunk surface.

**Keywords:** scoliosis, brace, spine deformity, spine stress state, computer aid brace design

### Introduction

Spinal corrective braces are used for treatment of spine scoliosis of children (pathologic deformation of the chest curve). The X-ray of the patient with scoliosis and with the brace is shown in **Fig. 2.** The dynamic corrective braces of type Cheneau or according to Cerny's patent No. 281800CZ (see **Fig. 1**) are usually used in the Czech Republic. The breast curve

can be classified according to King. The brace of type Cheneau is recommended for the spinal curve of type King I, II, and IV and the brace of type Černy for the spinal curve of type King II, III a V.

If the brace pushes the child trunk and on an appositive side is a hole then a stress state is in the patient's spine and the spinal pathologic form is corrected. After a long–term use of the brace, the part of spinal correction is permanent.

The brace is made in the following manner: a plaster negative form is made the first, and then the positive form of the child trunk. The orthopaedist's assistant according to X-ray of spine deepens the plaster positive form in the place where the brace has to push and labels on an appositive site the place for hole at the brace. The plastic brace is then made according to this plaster form. After its application on the child trunk the brace pushes at the places where the form has been deepened (the tight shoe principle) and moves the trunk to the brace hole.

The brace force effect can be the result of the orthopaedist and his assistant's experience only. This paper shows a computer aid design of brace form and calculation algorithms for vertebrae and inter-vertebrae discs stress, deformation and trunk surface load for the concrete brace applications.

The remodelling of the spine pathologic curve depends on the type of spinal defect, spine stress state, time and manner of the brace application. The aim of the

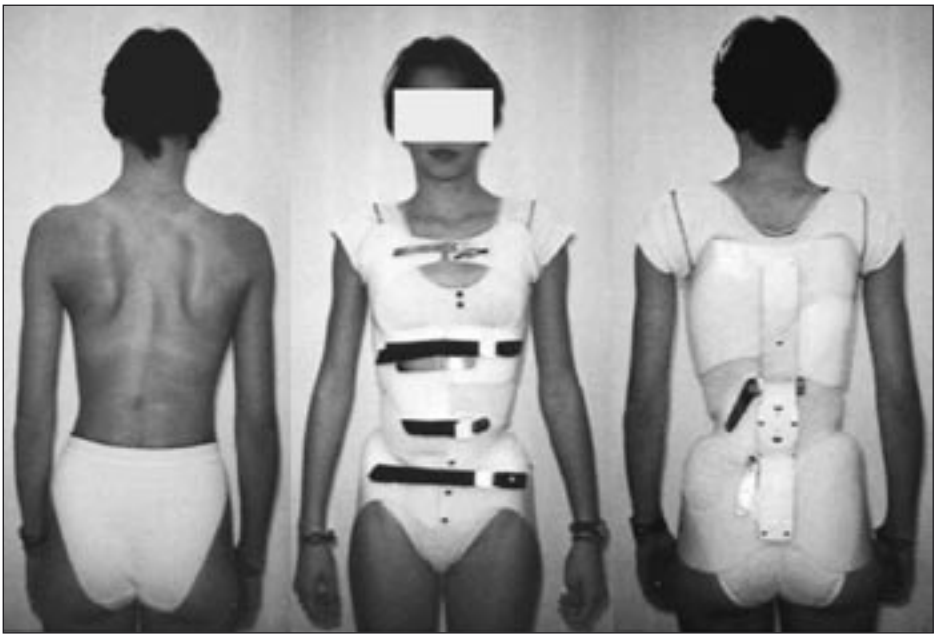

**Fig. 1.** Patient without and with the dynamic corrective brace according to Cerny (patent No. 281800CZ).

research is the determination of an ideal brace form.

## Spinal curve approximation

The spinal curve at the frontal plane is given by the function

$$y = y(x) \tag{1}$$

where $x$ is axis linking spine start and end at X-ray, $y$ is spine positions at frontal plane. The extreme values $y$ is measured on the X-ray (the extremes of the spinal axis curve in the left X-ray in **Fig. 2**) and the spinal curves (1) are constructed as polynomial approximation between the extremes.

The positions and values of extremes of spinal curve are measured at X-ray. Between the extremes is spinal curve approximated by polynomials. The polynomials are given by zero values at star and end, extreme values and zero derivates at places of extremes. The polynomial for the 1st segment has form

$$y = \frac{y_i}{l}\xi\left(2 - \frac{\xi}{l}\right) \tag{2}$$

for middle segment

$$y = y_{i-1} + \frac{(y_i - y_{i-1})\xi^2}{l^2}\left(3 - 2\frac{\xi}{l}\right) \tag{3}$$

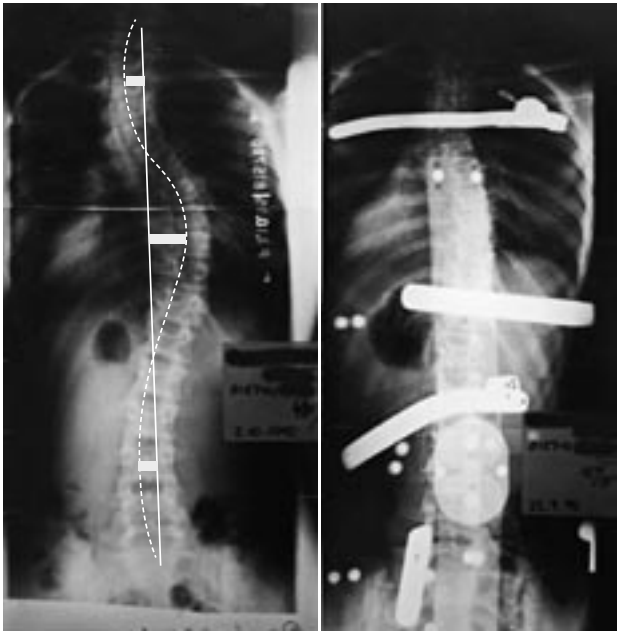

**Fig. 2.** The frontal X-ray of the patient from fig. 1 without and with the corrective brace.

and for last segment

$$y = y_{i-1}\left(1 - \frac{\xi^2}{l^2}\right) \tag{4}$$

where $y_i$ are measured extremes and $l$ is segment lengths (see **Fig. 2**). The values $y$ at the vertebrae centers are calculated according to these functions.

Spine stress state and deformation

The schema of patient trunk load is at **Fig. 4**, where $L$ is observed length of spine, the plaster positive form was depended at place $l_2$, $l_4$. The loads at these places are parabolic with the given maximum values $f_2$, $f_4$ at their centers. The positions of the depending parts are chosen with center at spinal axis extremes (see coordinates $L_1$, $L_2$, $L_3$ at the **Fig. 4**). The loads at parts $l_1$, $l_3$, $l_5$ are equal to reaction of patient trunk to the brace load.

The parabolic load (**Fig. 5**) is given by function

$$f = -\frac{p}{l}\eta^2 + p\eta\,, \text{ where } \; p = \frac{4f_i}{l} \tag{5}$$

From (5) can be calculated

$$f'(0) = -f'(l) = p = \frac{4f_i}{l} \tag{6}$$

Load schema at part $l_3$ is considered to be at points *a, b* the same tangent on the boundary of parts $l_2$, $l_3$ and $l_3$, $l_4$. It means that according to (6) are

$$f'_a = \frac{4f_2}{l_2}, \; f'_b = \frac{4f_4}{l_4}$$

The load at the interval *ac* consists from parabolic load (5) with $f_i = f_{a3}$ and linear load (see **Fig. 5**)

$$f = \frac{f_1}{l}\eta, \; f_1 = f_{03}$$

and at the interval *cb* from the same parabolic load and linear load

$$f = f_2 - \frac{f_2}{l}\eta, \; f_2 = f_{03}$$

where

$$f_{a3} = \frac{l_3}{16}\left(f'_a + f'_b\right), \; f_{03} = \frac{l_3}{4}\left(f'_a - f'_b\right) \tag{7}$$

The load $f_1$, $f_5$ can be determined from moment equilibrium equation to centres of parts $l_1$, $l_5$ according to **Fig. 4.**

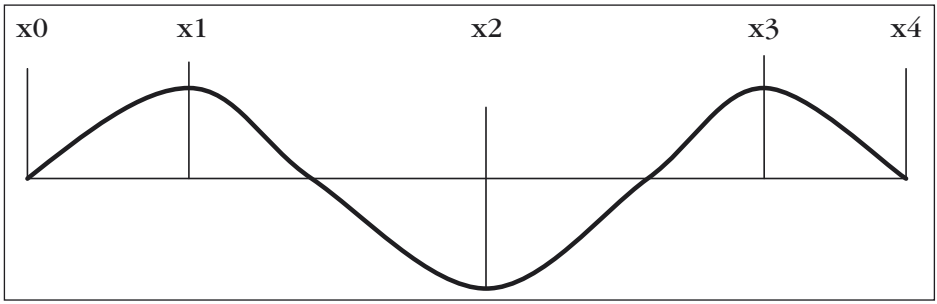


**Fig. 3.** X- ray ... measured extremes of the spinal axis curve.

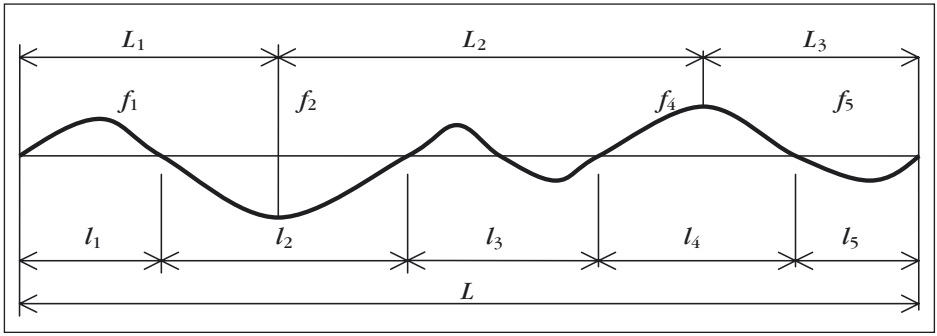


**Fig. 4.** Parabolic loads of parts of patient trunk..

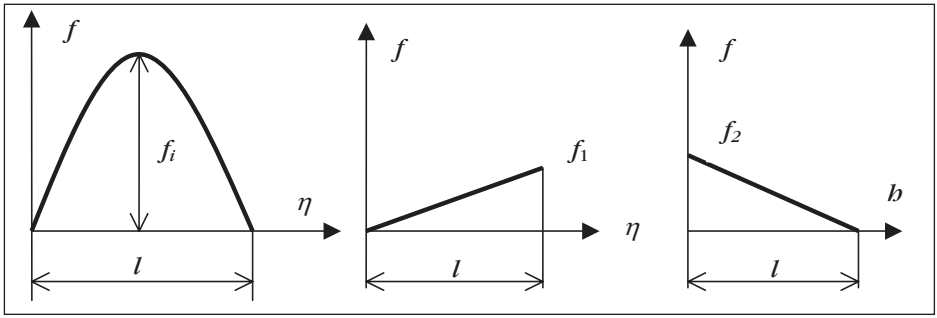


**Fig. 5.** Parabolic and linear load..

$$f_1 = \frac{f_2 l_2\left(\frac{l_2}{2}+l_3+l_4+\frac{l_5}{2}\right) - f_{a3}\frac{l_3^2}{4} - \frac{3}{4}f_{03}l_3\left(\frac{l_3}{2}+l_4+\frac{l_5}{2}\right) - f_4 l_4\left(\frac{l_4}{2}+\frac{l_5}{2}\right)}{l_1\left(\frac{l_1}{2}+l_2+l_3+l_4+\frac{l_5}{2}\right)} \quad (8)$$

$$f_4 = \frac{f_4 l_4\left(\frac{l_4}{2}+l_3+l_2+\frac{l_1}{2}\right)-f_{a3}\frac{l_3^2}{4}+\frac{3}{4}f_{03}l_3\left(\frac{l_3}{2}+l_2+\frac{l_1}{2}\right)-f_2 l_2\left(\frac{l_2}{2}+\frac{l_1}{2}\right)}{l_5\left(\frac{l_1}{2}+l_2+l_3+l_4+\frac{l_5}{2}\right)} \tag{9}$$

Shear force $Q$ and bending moment $M$ can be determined by integration of the differential equations

$$Q' = -f \text{ and } M' = Q$$
$$Q = Q_1 + \frac{p\eta^3}{3l} - \frac{p\eta^2}{2} - \frac{f_1\eta^2}{2l} - f_2\eta + \frac{f_2\eta^2}{2l} \tag{10}$$

$$M = M_1 + Q_1\eta + \frac{p\eta^4}{12l} - \frac{p\eta^3}{6} - \frac{f_1\eta^3}{6l} - \frac{f_2\eta^2}{2} + \frac{f_2\eta^3}{6l} \tag{11}$$

where $Q_1$, $M_1$ are values at beginning of parabolic load and η is a coordinate according to **Fig. 5**, $f_1$ is equal $f_{03}$ at interval *ac* of part $l_3$ and otherwise is zero, $f_2$ is equal $f_{03}$ at interval *cb* of part $l_3$ and otherwise zero.

The spine is considered stiff at vertebra places and elastic at inter-vertebrae parts. The spinal axis turning φ and horizontal displacement $w$ are calculated from differential equations

$$EI\varphi' = M, \quad w' = \varphi \tag{12}$$

The turning φ and displacement $w$ at vertebra place ($E \to \infty$) are

$$\varphi = \varphi_0, \quad \mathrm{w} = \mathrm{w}_0 + \varphi_0\xi \tag{13}$$

where $\varphi_0$, $w_0$ are values at the beginning of solved interval and ξ is an interval coordinate. The turning φ and displacement $w$ at inter-vertebrae part are according to (12) and using (11)

$$\varphi = \varphi_0 - \frac{1}{EI}\left[M_1 a_1 + Q\frac{a_2}{2} + p\left(\frac{a_5}{60l} - \frac{a_4}{24}\right) - f_1\frac{a_4}{24l} - f_2\left(\frac{a_3}{6} - \frac{a_4}{24l}\right)\right] \tag{14}$$

$$w = w_0 + \varphi_0\xi - \frac{1}{EI}\left[M_1\frac{a_2}{2} + Q_1\frac{a_3}{6} + p\left(\frac{a_6}{360l} - \frac{a_5}{120}\right) - f_1\frac{a_5}{120l} - f_2\left(\frac{a_4}{24} - \frac{a_5}{120l}\right)\right] \tag{15}$$

$$a_i = \eta^i - \eta_0{}^i$$

where $w_0$, $\varphi_0$ are the values at beginning of solved interval, $M_1$, $Q_1$ are the values at beginning of parabolic load, $\xi$ is a coordinate from the beginning of solved interval and $\eta$ is a coordinate from beginning of parabolic load. The moment of inertia $I$ of inter-vertebrae cross section can be determined as sum of triangles. The values need not be determined for each patient but they can be calculated for one patient and for concrete patient recalculated according to a scale. The patient with lumbar vertebra bright 5 cm at frontal plane has moment of inertia $I = 26.0044$ cm$^4$ (axis at sagital direction). The patient with vertebra width $h$ has

$$I = 26{,}0044h^4/625 \tag{16}$$

Each inter-vertebrae part can be considered correctly with different cross section characteristic $I$ or less correctly and easier by a constant values of $I$ for all inter-vertebrae parts. The influence of the less thoracic vertebrae diameter is eliminated by bending resistance of ribs.

The differential equations (12) will be solved step by step at vertebrae and inter-vertebrae parts. The height of vertebrae can be measured on X-ray or judge from observed length of spine interval $L$ and number of vertebrae $n$ at this interval. The average thin of inter-vertebrae discs is

$$a = \frac{L}{6(n-1)}$$

The average height of vertebra is

$$h_{average} = \frac{L-(n-1)}{n}$$

The height of concrete vertebra is (the vertebrae are numbered at superior direction)

$$h_i = h_{average} + \frac{0{,}2h_{average}}{n-1}\left(\frac{n-1}{2} - i - 1\right)$$

The vertebra number has to be set as real number.

The calculation starts with initial conditions $w_0 = 0$, $\varphi_0 = 0$, $M_0 = 0$, $Q_0 = 0$ and it is repeated at all vertebra and inter-vertebrae intervals. The results $w_{ip}$ $\varphi_{ip}$ $M_{ip}$ $Q_i$ at end of intervals are calculated according to formulas (13) to (15) and (10), (11). The calculated values at the interval end are used as initial conditions at the next interval. The final value at the last interval is $w_f$. Now the initial condition $\varphi_0$ must be corrected to be the final value $w_f = 0$.

$$\varphi_0 = -\frac{w_f}{l}$$

The all calculation can be repeated with the new initial condition $\varphi_0$ or the values $w_{ip}$ $\varphi_i$ can be corrected in this way

$$w_{i,nové} = w_i + \varphi_0 x, \quad \varphi_{i,nové} = \varphi_i + \varphi_0$$

where $x$ is distance from origin of the first interval.

## Optimal value of load

The ideal correction at all centers of vertebrae $w_{i,ideal}$ are values calculated from (2) to (4) with appositive sign.

The load values $f_2$, $f_4$ will be search to be quadratic error of ideal correction at the vertebra centers $w_{i,ideal}$ and calculated values $w_i$ for the values $f_2, f_4$ minimal, it means to be minimal value

$$\varepsilon = \sum_{i\%1}^{n} (w_i - w_{i,ideal})^2 \tag{17}$$

The values $f_2, f_4$ will be searched by method of maximal slope of error ε with numerical calculation of partial derivations. The step of numerical calculation will be halved if the error ε is not less then previous error. Each error is stored which was lesser the previous one. The calculation is finished if the steps $step_1$, $step_2$ of loads $f_2, f_4$ (occurrence of loads) are less then the given value. Because the calculated spinal curve has not the same form as ideal correction curve the final error ε will not be zero.

Let's show the calculation algorithm for determination of optimal values of loads $f_2, f_4$. The calculation of values of parabolic loads $f_1, f_{a3}, f_{03}, f_5$ for given values $f_2, f_4$ and solving of differential equation (12) using beam theory and calculation of error ε from (17) is designated "solving of error ε".

1. Choice of initial values according to previous experiences: $f_2, f_4$, $step_1$, $step_2$
2. "solving of error $\varepsilon_{old}$"
3. Cycles: for $i$ = 1 to 50; for $j$ = 1,2
4. $f_{old,j} = f_{2xj}$; $f_{2j} = f_{2xj} + step_j$
5. "spine solving(ε)"
6. $S_j = \varepsilon - \varepsilon_{old}$; if $S_j > 0$ then ($S_j = -S_j$; $step_j = -step_j$, $f_{2xj} = f_{old,j}$ )else ($\varepsilon_{old,j} = \varepsilon$, $f_{old,j} = f_{2xj}$)
7. Repetition of cycle $j$
8. $S_{total} = \sqrt{(S_1^2 + S_2^2)}$ ; $f_2 = f_2 - step_1 * S_1/S_{total}$; $f_4 = f_4 - step_2 * S_2/S_{total}$
9. "solving of error ε"
10. If $\varepsilon > \varepsilon_{old}$ then ($f_{1,old} = f_2$; $f_{2,old} = f_4$; $step_1 = step_1/2$, $step_2 = step_2/2$; else $\varepsilon_{old} = \varepsilon$)
11. if $\sqrt{step_1^2 + step_2^2}$ < given occuracy then stop and output of $f_2, f_4$

12. Repetition of cycle *i*

13. Stop and message "Given accuracy was not be reached"

## Conclusion

The algorithms were verified with data base of cured patients at Ambulant Centre for Defects of Locomotor Aparatus (Ivo A. Mařík, M.D., Ph.D., F.A.B.I.) and ORTOTIKA a.s. (Eng. Pavel Černý).


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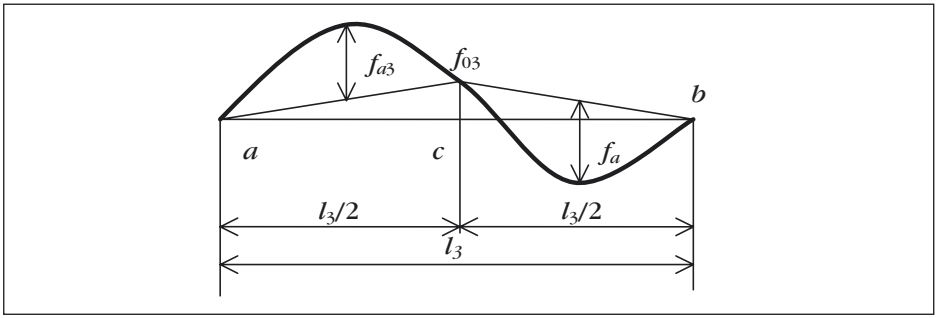


**Fig. 6.** Load schema at part $l_3$.

**ORIGINAL PAPER**

## REMODELLING OF A LIVING BONE – NUMERICAL SIMULATION

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### Abstract

The capacity of bone to adapt to functional mechanical requirements has been known for more than a century, and many theoretical and experimental models have been developed for bone remodelling. However, these models are still not able to sufficiently predict its behaviour. In our report, a thermodynamic model based on knowledge of biochemical control mechanisms of bone remodelling process is presented. Its formulation is based on nonequilibrium thermodynamics and was mathematically analysed. Despite the complexity of the regulatory system of bone adaptation, the calculated results are in very good correlation with the experimental observations. With the aid of this model, the whole inner structure of bone can be elucidated. The model is also able to simulate influence of dynamic loading, i.e. impact of amplitude, frequency, and direction of acting forces, together with biochemical factors, e.g. the fundamental RAKL-RANK-OPG pathway. The simulation results coincide with observed behaviour of the bone remodelling process. The great advantage of used thermodynamic approach is that it connects all the involved disciplines: mechanics, biology, chemistry, osteology and mathematics. Hence we may simulate the influence of biochemical factors together with mechanical ones.

**Key words:** bone remodelling, RANKL-RANK-OPG pathway, dynamic loading, biochemical model, mathematical modelling

When mechanical stresses are placed upon bone, it remodels in order to withstand the stresses. The induced processes may also be considered to be driving forces of a structural changing. These processes systematically, iteratively, and continually eliminate and redistribute osseous material throughout the domain to obtain an optimal arrangement of internal bony structures.

To find the coupling between bone structure formation and applied external mechanical load is the main problem of the bone structure remodelling process. It is the main goal of this talk to introduce one possible formulation and consequent calculation of the above physiological and biochemical processes.

With the development of computer-aided strategies and based on the knowledge of bone geometry, applied forces, and elastic properties of the tissue, it may be possible to calculate mechanical stress transfer inside a bone (FE-analysis). Assuming the above mentioned structural optimization process, the change of stress in particular compartments of the bone should further be followed by internal bone density distribution. This logical consequence allows us to think about mathematical models that can be used to study functional adaptation quantitatively, and furthermore to create the mineral

bone density distribution patterns. Similar mathematical models have been built in the past. Since they calculate just mechanical transmission inside the bone and not considering humoral cell-biologic factors of bone physiology, they just only partially correspond to reality seen in living organisms and cannot explain either mechanical loading or medical treatment (**1**), (**2**). The aim of following mathematical model is to combine the biological factors with biomechanical ones. Such model may also reflect changes in remodeling behavior corresponding to pathological changes of the bone metabolism.

Bone remodelling (BR) occurs when the populations of bone cells break down old bone and replace it with new bone. This reformation results in the reorientation of internal bone structure and eventually in changing the shape of the bone, which means that bone can better adapt to the loads that are being placed upon it. Loads on bone cause mechanical strains and even micro-damage generating signals that specific cells can detect and to which they or other cellular populations respond (mechanical stimuli to local cells was considered critical for the bone adaptation process (**3**), and this interaction was later described by Heřt in 1970s (**4**)). Actually, remodelling depends on time-varying straining. Because of the viscoelastic properties of bones, the strains vary not only under varying loading but the strain changes continue and fade as the elastic after-effects at constant load and after unloading. In this manner, the existence of remodelling effects even at rest can be explained (**5**).

The signaling and subsequent change in cellular phenotype may be called activation and represents the first stage of the remodeling process. The aim of activation is to prepare sufficient pool of executive cells concentrated in the domain of the old bone that is to be repaired. The original bony structures (*Old_B*) infracted by the initiating biomechanical stimuli (microdamages) are intended to be absorbed and subsequently replaced by the new bone (*New_B*), see **Fig. 1.**

The generated bone mass will be structurally and morphologically adjusted to the new mechanical loads. These two phases, described as resorption and formation, accomplish the whole process of remodeling. Biology of the bone remodelling itself is not completely understood in this moment (**6**). Frost has defined the minimum effective strain – neither apposition nor resorption below 1500–2500 microstrains. According to Frost (**7**), the strains above that threshold level affect modelling and remodelling activities in ways that change the size and configuration of growing bones, tendons, ligaments and fascia to their new mechanical usage and return their strains to the threshold level. Recently, the control mechanism between resorption and formation of bone was described, by so called *RANKL-RANK-OPG* pathway (**6**), (**8**), and our mathematical model covers the crucial moments (based on chemical description of bone remodelling process (**9**)).

System of basic (or bone) structural units (BSU) is widely accepted for bone remodeling description (**10**), (**11**). This concept is very suitable for the investigation of bone tissue remodeling by numerical methods, eg., finite elments or finite volume methods. Each such BSU contains enough of local populations of osteocytes, osteoblasts (*OB*), and of mononuclear osteoclast precursors (*MCELL*) to carry out the bone remodelling process. Osteocytes

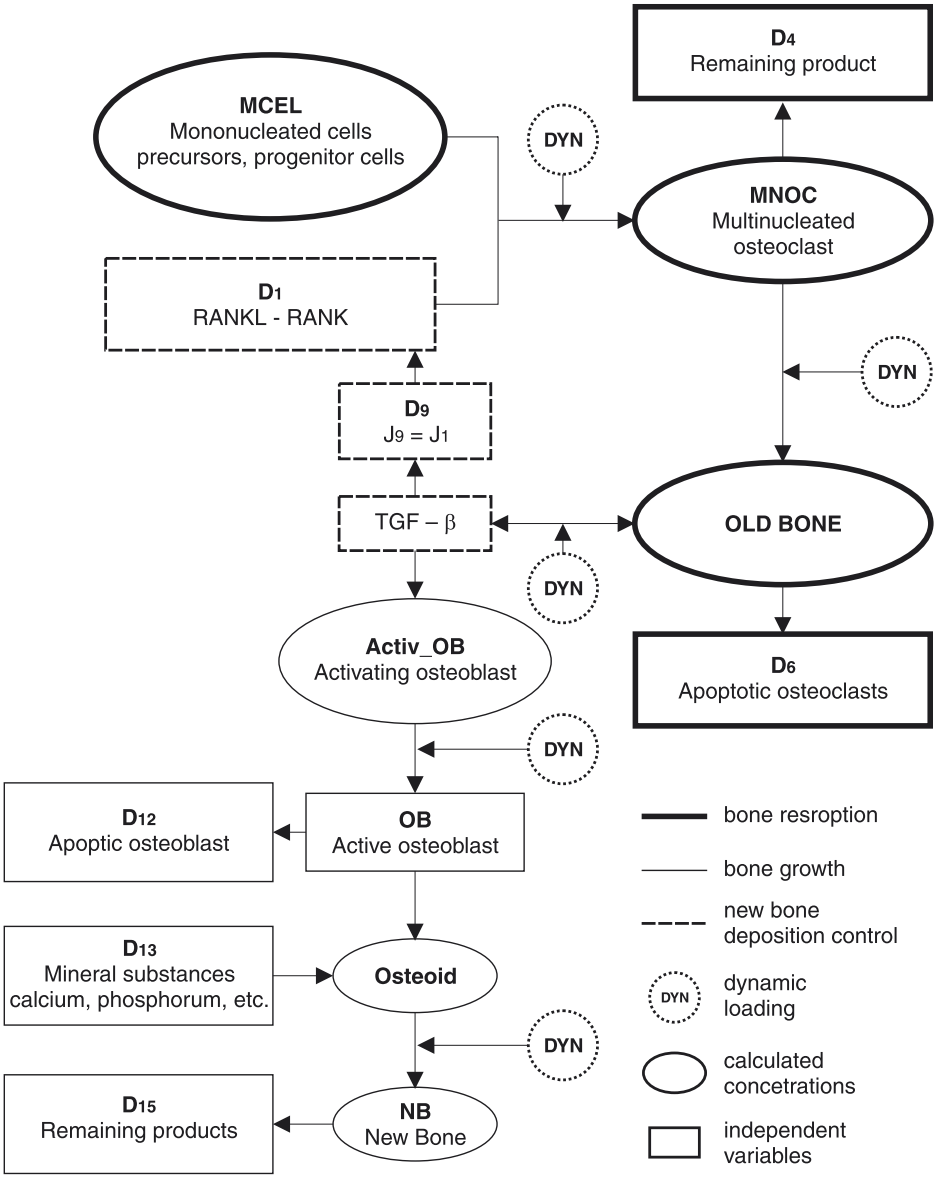


**Fig. 1.** Simplification of bio-chemical proceses relevat for bone remodeling induced both mechanical and biochemical effects.

are presumed to react to mechanical strain either piezoelectrically through ionic currents induced when bone is deformed or by detecting fluid flow in the periosteocytic lacunas. They respond to this strain by sending signals that activate bone formation or existing bone removal. During the activation, *MCELL* turn to multinucleated osteoclasts (*MNOC*) having high metabolic activity. *MNOC*s are charged with resorption of the old bone and the defect is subsequently filled with osteoid – non mineralized bone matrix produced by activated osteoblasts (*OB*) that during next 5–15 days becomes mineralized.

Bonds between *RANK* and its ligand *RANKL*, denoted as $D_1$, are dominant for bone resorption process. The enhancement of *OPG* causes decrease of $D_1$ (since OPG binds with high affinity to *RANKL* and thus disables binding of *RANK* to its ligand) and thus also decrease of osteoclasts activity, and in opposite the decrease of *OPG* results in the increase of osteoclasts activity and consequently to bone lose. The imbalance of *RANKL/OPG* ratio causes the initiation of reaction with mononuclear haematopoietic cells (*MCELL*), which enhances the concentration of mononucleated osteoclasts (*MNOC*). *MNOC* is a mixture of precursors of osteoclasts and active osteoclasts. Remaining product $D_4$ is not further used. In total, the bone decomposition can be described by the two following kinetic equations

$$D_1 + MCELL \xleftrightarrow{k_{\pm 1}} MNOC + D_4, \tag{1}$$

$$MNOC + Old\_B \xleftrightarrow{k_{\pm 2}} TGF + D_6. \tag{2}$$

*TGF* indicates the family of cytokines, which influences haematopoietic stem cells to differentiate into macrophages or other related cell types, e.g., macrophage colony-stimulating factor (M-CSF), or transforming growth factors (e.g., bone morphogenetic proteins-BMPs like TGF-β, etc), which take place during *Old_B* resorption and *New_B* deposition (**6**). $D_6$ is a remaining product.

Before osteoblasts (*OB*) secret collagen in hollowed cavity, they need first to be activated. Osteoblasts are derived from mesenchymal stem cells, which can give rise to myoblasts, adipocytes, and chondrocytes (**6**). This activator (*Activ_OB*) is being produced after resorption in given volume (cavity). Thus following reaction scheme can represent behaviour of osteoblasts at specific site:

$$TGF + Old\_B \xleftrightarrow{k_{\pm 3}} Activ\_OB + D_9, \tag{3}$$

$$Activ\_OB + OB \xleftrightarrow{k_{\pm 4}} Osteoid + D_{12}, \tag{4}$$

where $D_9$, $D_{12}$ are remaining productes.

The longest period in bone remodelling process pertains to mineralization (deposing calcium, etc. – $D_{13}$ – into matrix) of osteoid:

$$D_{13} + Osteoid \xleftrightarrow{k_{\pm 5}} New\_B + D_{15}, \tag{5}$$

where *New_B* denotes new bone formed by remodelling process and $D_{15}$ is the residuum of bone formation reaction.

These chemical equations – to – describe the essential processes of bone remodelling. There are 15 substances involved, and by using the law of active mass and adding the external fluxes, 5 differential equations describing the whole system can be obtained. By solving these kinetic equations, time evolution of *MCELL*, *Old_B*, *Activ_OB*, *Osteoid*, *New_B*, concentrations are obtained. All the remaining can be calculated.

The above model of bone as a living material that is routinely exposed to mechanical influence causes its structural configuration. To estimate the effect of mechanical loads locally it is needed to know the stress-strain fields in the investigated bone section. These are calculated from balance of forces and momentum in real bone geometry under real loading condition that occur during walking of an adult man. Then, using presented model, elastic properties of each BSU can be adjusted to loading condition. Elastic properties modify according to changes in apparent bone density distribution and the later varies with different loading condition in particular BSU:

$$C^{ijkl} = C^{ijkl}\left(Old\_B, New\_B\right) = C^{ijkl}\left(Old\_B\left(d_{(1)}\right), New\_B\left(d_{(1)}\right)\right),$$

where $d_{(1)} = \mathrm{div}\left(\mathbf{v}\right) = \frac{\partial v_1}{\partial x_1} + \frac{\partial v_2}{\partial x_2} + \frac{\partial v_3}{\partial x_3} = -\frac{1}{\rho}\frac{\mathrm{d}\rho}{\mathrm{d}t}$ is the trace of the rate deformation tensor.

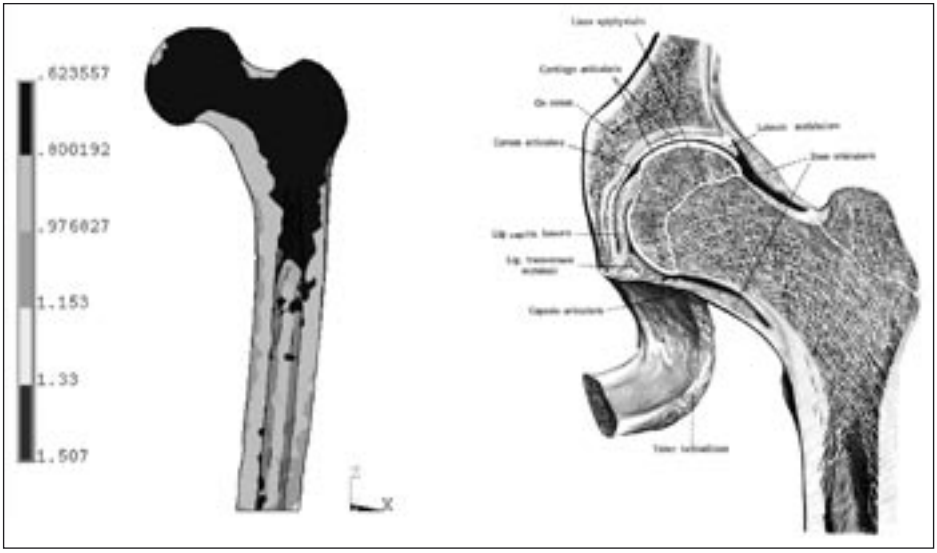


**Fig. 2.** Calculated apparent density distribution for a proximal femur – left – and actual bone tissue distribution in human femur – right (notice correspondence in the patterns).

When applying all here mentioned pieces of knowledge you will get a following simulation of bone remodelling process in human bone (namely in proximal femur), see **Fig 2.**

More details and features of mentioned model will be presented together with more precise description and other numerical results (simulations).


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**PERSPECTIVE ARTICLE**

# DYNAMIC STABILIZATION OF THE SPINAL FUNCTIONAL UNIT LET'S GO BACK TO JFK CASE


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## Summary

In summary our experience with utilization of dynamic stabilization of the spine in the cervical and lumbar region opens new opportunities in spinal surgery. It is however worth remembering, that the concepts that are valid for, and methods developed for large, synovial joints arthroplasty may not fully apply to a typical spi-

nal mobility unit composed of 2 synovial articulations and 2 or 4 articular surfaces. It may happen that it will be necessary to verify the present concepts emerging from the understanding of the role of mobility preservation in spinal surgery.

**Key words:** dynamic stabilization, spinal surgery, spinal functional unit, cervical and lumbar region

## Introduction

The 40th aniversary of the first presentation of replacement of a lumbar intervertebral disc with an artificial prosthesis. Fernstrom described an operation in which in place of a removed intervertebral disc a steel ball was implanted. This has been the first artificial disc (**1**). One of the first patients receiving this treatment was the USA president, John Fitzgerald Kennedy.

This already dated concept of spinal segment (FSU – functional spinal unit) stabilization with preservation of mobility is finding acceptance in clinical practice not without difficulty.

During those 40 years many technical options for immobilization of spinal segments were developed. Existing surgical approaches to the spine were modified and new approaches designed. Technological progress and increasing understanding of biomechanics of the spine were used to develop effective spinal fusion. The efforts were concentrated on development of a possibly stable and rigid connection between the adjacent vertebrae.

Concurrently developed surgical methods of joint surgery were based on introduction of technique capable to restore full mobility of the damaged joint. They found their way into everyday use. Arthroplasty of the hip or knee joint are a common practice.

## Material

During the last 3 years surgical methods preserving spinal mobility were utilized in the Department of Neurosurgery and Pediatric Neurosurgery in Lublin.

Out of 850 spinal operations performed last year (2006) in 420 cases various types of spine stabilizing implants were used. Among those only 81 implanted devices secured preservation of the spinal segment mobility. Still this is a remarkable increase in the number of those operations since in the year 2004 there were only 2 such procedures done.

## Operation methods and discussion

The argumentation supporting use of the more complex and expensive mobility securing devices in spinal stabilization indicates possibility of a reduction of mechanical stress to the adjacent spinal segments and preservation of a greater range of movement.

There are differences in the indications for and surgical procedures used in the management of diseases of the various segments of the spine.

In cervical spine the most common operation is discectomy followed in the great majority of cases by spondylodesis of vertebral bodies. Many investigators indicate that fusion plays an important role in achieving good results of surgical treatment of cervical disc disease (**2**).

There is not yet an adequate body of literature proving that use of an artificial disc in place of a rigid fusion in cervical spine is superior in long term. This is to

some extent the result of a great variety of artificial discs and modifications of surgical indications, which reduced the volume of patients treated in the same manner. There are however papers describing good early clinical outcome of implantation of an artificial disc, confirming preservation of mobility in the diseased segment and reduction of degenerative changes in the adjacent spinal segments (**3**).

We have implanted 13 artificial discs at the level of C4/C5 and C5/C6 in the treatment of patients suffering degenerative disc disease. There were no complications.

Short term observation (mean 5.5 months) of 13 cases proves that the procedure is safe and cervical spinal mobility remains unaffected.

The technical execution of the procedure does not require long training and can be performed by surgeons experienced in operating on the cervical spine from an anterior approach. The operation takes only a little longer than classical interbody fusion with artificial implants. In our experience the average time of single level discectomy with artificial disc implantation took only 20 minutes longer then discectomy with fusion.

There is a variety of artificial disc constructions available. All presently used devices offer mobility in three planes. We used three types of artificial discs: Bryan, Prestige LP, Prodisc C. Due to a limited number of cases and lack of randomization so far we did not analyze the differences in the treatment results in relation to the type of prosthesis used. We did not encounter any important difficulties in the surgical procedures required in the implantation of any of those artificial discs. In all cases patients were able to return to work and normal physical activities within mean 4.4 weeks (range 4-6 weeks). It has to take into account that the patients in whom artificial disc was implanted were a selected group of relatively young, professionally and physically active persons, sportsmen, trainers. This group is known to have better early prognosis in spinal surgery.

Another group of patients treated in whom dynamic stabilization was used were those with lumbar spinal disease. Like in the cervical region similar principles of surgery are applied in the treatment of lumbar spine. Total disc replacement is used in the treatment of degenerated intervertebral disc when there is compression of the nervous elements. An artificial device implanted between vertebral bodies into the intervertebral space provides for certain degree of mobility in the operated segment.

This type of operations has been described in many publications and is actively promoted by implant producing industry. The results of treatment and indications for artificial lumbar disc replacement are still a mater of debate and controversies.

Even with the encouraging results published from many centers the indications for this treatment has not been well defined and complications may be serious, even life threatening (**4**).

The operation is complex and requires special training to become acquainted with a new anterior trans- or retroperitoneal approach to the lumbar spine. For many spinal surgeons this is a new anatomical territory with fragile structures and long approach routes. New disc prosthesis that could be implanted retroperitoneally from a lateral approach could extend indications for this procedure. This approach should not increase surgical risk beyond

that of contemporary method of treatment of degenerative lumbar disc disease.

Indications commonly proposed for the use of artificial lumbar disc implantation dedicate this treatment mainly to young, physically active men. In this particular group of patients one of the complications, impotency resulting from intraoperative damage to the lumbar plexus, is reported in up to 14 % of cases and is a particular snag (**5**).

Dynamic posterior interosseous stabilization represents another dynamic method used in operations of the lumbar spine. The main indications is intervertebral disc bulging with foraminal stenosis, disc protrusion with spondyloarthrosis, conflict between adjacent spinal processes concomitant with disc degeneration. Implantation of an elastic element between the spinal processes changes relative positioning of the vertebral bodies thus changing mechanical stress distribution in the intervertebral disc and intervertebral joints. The implanted device adds a new posterior elastic component to the Junghans mobility unit (**6**).

In the last year 62 operations with 1 or 2 Devices for Intervertebral Assisted Motion (DIAM) were performed on patients that were candidates for disc removal which would result in rigid segment spondylodesis. Applying strict indication criteria for this operation and meticulous surgical procedure excellent and good results were achieved in 58 patients. There were no serious complications.

Preservation of spine mobility is based not only on mobile or elastic implants. It requires careful selection of stabilization technique to limit the range of movement. This concept is well represented by C1–C2 segment stabilization without cervico-occipital fusion used in a variety of pathologies of the cranio-cervical junction. Operations described by Magerl and Harms permit stiff and safe connection without risk of pseudoarthrosis and preservation of head mobility (**7**).

Similar benefits offer posterior cervical stabilization through the lateral mass instead of commonly used hooks attached to the vertebral arches. New method allows fixation at the level of decompression without need to attach of an implant one level above and below it, thus making them immobile (**8**).

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**CASE REPORT**

# APPLICATION OF ULTRASONOGRAPHY IN DIAGNOSTICS OF SOME PATHOLOGY PROBLEMS OF MUSCULOSKELETAL SYSTEM IN CHILDREN

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## Summary

In some cases the pathological changes of musculoskeletal system cannot be visualized on plain x-ray films. Than it is necessary to extend diagnostics and apply other methods such as ultrasound examination or MRI. The aim of the study was to evaluate, on the basis of chosen cases, the usefulness of ultrasonographic examination in children in the diagnostics of changes within musculoskeletal system, which are not visible on x-ray films.

Ultrasonographic examinations were performed in four children with clinical symptoms of musculoskeletal injuries, and with no changes on conventional x-ray examinations.

All children complained of knee region pain, three of them were after trauma and one without traumatic anamnesis.

In all examined children, ultrasonographic examinations enabled diagnosing pathological changes of musculoskeletal system such as: the Osgood-Schlatter disease, avulsion fracture of insertion of medial collateral ligament, osteochondral loose body, foreign body.

**Key words:** Ultrasound, X-ray films, Musculoskeletal system

## Introduction

In the estimation of pathological changes of musculoskeletal system in children, a starting diagnostic algorithm method is constantly a classical x-ray examination.

It is known, that in some cases the pathological changes cannot be visualized on plain x-ray films. It concerns particularly changes within muscles, tendons, ligaments and chondral parts of bones.

In these cases it is necessary to extend diagnostics and apply other methods such as MRI or CT. At present, more and more frequently ultrasonographic examinations are also performed.

## The aim

The aim of the study was to evaluate, on the basis of chosen cases, the usefulness of ultrasonographic examination in children

in the diagnostics of changes within musculoskeletal system, which are not visible on x-ray films.

## Material and method

Ultrasonographic examinations were performed in four children with clinical symptoms of musculoskeletal injuries, and with no changes on conventional x-ray examinations.

All children complained of knee region pain, three of them were after trauma and one without traumatic anamnesis.

The examinations were performed using Philips IU 22 ultrasound scanner with high-resolution transducers of 7–17 MHz frequencies .

## Results

In all children, ultrasonographic examinations enabled diagnosing pathological changes of musculoskeletal system such as: the Osgood-Schlatter disease, avulsion fracture of insertion of medial collateral ligament, osteochondral loose body, foreign body.

The diagnoses were confirmed in two cases by arthroscopy and during surgical intervention, in the latter by successful conservative treatment.

## Conclusion

Ultrasonographic examinations are particularly useful in children in visualization of the musculoskeletal changes, which are not visible on conventional x-ray films.

Sonography is especially helpful in detecting and localizing of foreign bodies in joints or soft tissues.

## Introduction

The most often indications to begin an imaging diagnostics of musculoskeletal system in children are trauma, pain and limitation of motor activity. Usually, a conventional x-ray examination begins a diagnostic algorithm. However, in some cases the pathological changes of musculoskeletal system cannot be visualized on x-ray scans. Thus, in these cases, the extent of diagnostic methods must be widened. More frequently, in such cases, the ultrasonography is being used (**1, 2**). Main advantages of this method are: availability, non-invasiveness and possibility to analyze function of musculoskeletal system, what is particularly important in the diagnostics in children.

## The aim

The aim of the study was to evaluate, on the basis of chosen cases, the usefulness of ultrasonographic examination in children, in the diagnostics of changes within musculoskeletal system, which are not visualized on plain x-ray scans.

## Material and method

Ultrasonogrophic examinations were performed in four children with clinical symptoms of musculoskeletal system. In all cases conventional x-ray examinations did not visualize any pathological changes.

All children complained of knee region pain. Three of them were after trauma and one without traumatic anamesis.

The examinations were performed using Philips IU 22 ultrasound scanner with high-resolution transducers of 7–17 MHz frequencies.

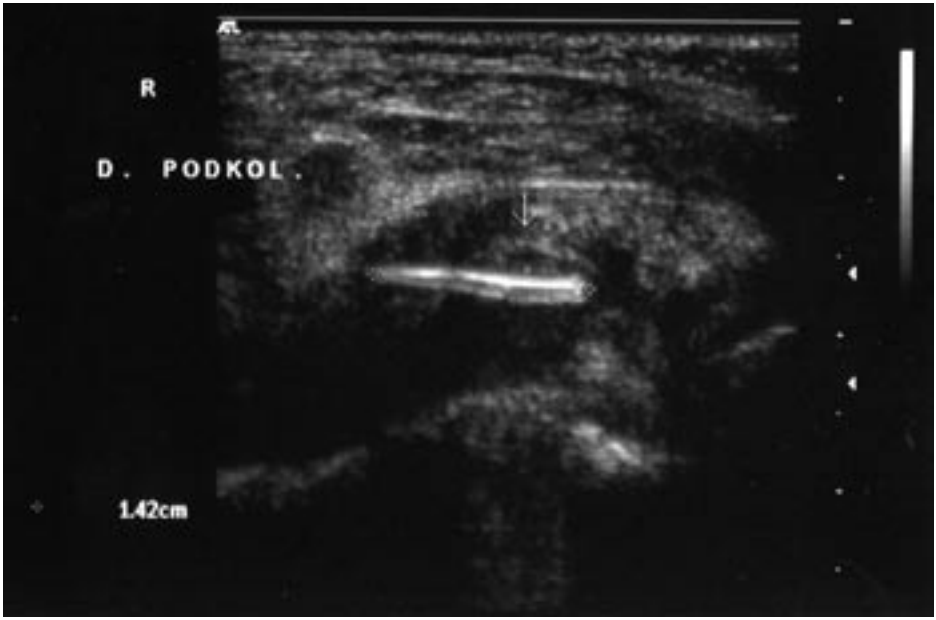


**Fig. 1.** Foreign body in subpopliteal region

## Case 1

A 12-year-old boy, sufferig from a penetrating trauma with sharp stick, which stuck in the knee joint from the anterior side. During trial of taking it out, the stick broke and its small piece remained within area of knee joint. Conventional radiography did not visualize any post-traumatic changes.

Ultrasound scan performed in a week and a half after trauma, indicated the presence of foregin body as linear hyperechogenicity of 15 mm lengh, placed below joint fissure of posterior side of articular capsule in the area of medial condyle of the tibia. Moreover, edema of Hoffy body and within, linear hypoechogenic structure fitting to post-traumatic changes were visualized. **Fig. 1.** Synovitis of high degree was also visualized.

The presence of foregin body within knee joint was confirmed by surgical procedure. The piece of stick was removed, and its localization and size were corresponding with sonographic findings.

## Case 2

A 11-year-old boy, complaining since a year ago on painfulness in the projection of left tibial tuberosity. In anamnesis, he did not recall any trauma at this area. On x-ray films, the area of tibial tuberosity and left knee joint was without visible changes. Sonographic examination showed an irregular contour of left tibial tuberosity, the presence of ectotopic calcification in this area, inflammatory changes in deep intrapatellar bursa and the presence of fluid in

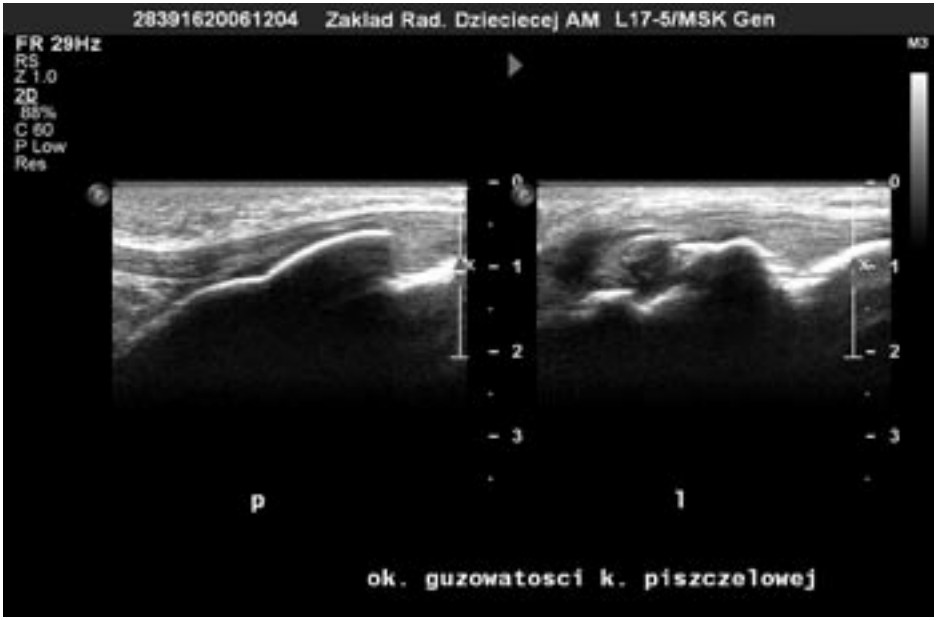


**Fig. 2.** The Osgood-Schlatter disease on the left side

it, thickened walls with increased blood vessel flow in Power Doppler examination.

Considering the results of sonographic examination, clinical picture and patient's age the Osgood-Schlatter disease was diagnosed and further diagnostics was unnecessary (**Fig. 2**).

## Case 3

A 16-year-old boy who experienced a knee injury with complete displacement of the patella two weeks earlier. Conventional radiography did not show any changes in the joint. The patient underwent the ultrasound examination of the knee in which hemarthrosis and a single one-inch osteochondral fragment was found (**Fig. 3**).

An arthroscopy confirmed the presence of free osteochondral fragment and showed the donor place on lateral patellar surface.

## Case 4

A boy, aged 16, with a pain in medial compartment of the knee. Two days earlier he had an injury of the right knee joint with valgus mechanism. The conventional radiography did not show any obvious changes. Only blurring of the contour of medial femoral condyle was seen. In an ultrasound examination the swelling of femoral attachment of medial collateral ligament and disruption of cortical bone in this place was observed. (**Fig. 4**)

One fragment of cortical bone was elevated. Based on these findings the dia-

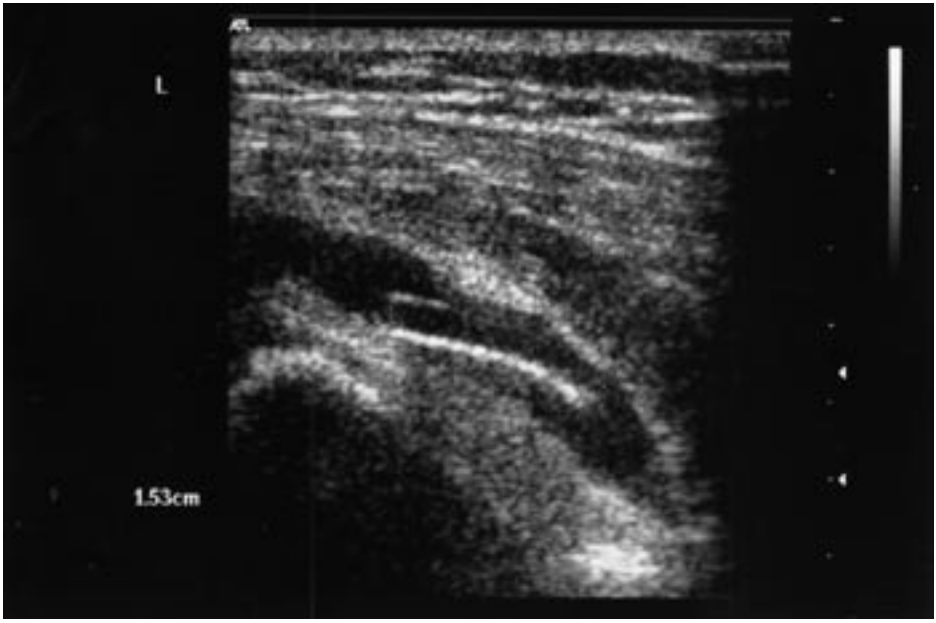


**Fig. 3.** The osteochondral loose body in the knee joint

gnosis of avulsion fracture of medial collateral ligament was made and other imaging modalities were not performed. The patient was treated in a conventional manner.

## Results and discussion

Foreign bodies absorbing x-ray radiation in the same degree as human soft tissues are not visualized on x-ray scans. These may be the materials such as wood, plastic and glass, which are the most frequently extracted foreign bodies from soft tissues in children after trauma.

Sonography allows to visualize foreign body independently of its structure. Usually, foreign bodies are visualized on ultrasound scans as a structure with hyperechogenic contours (**3**).

In presented case, a piece of stick invisible on the x-ray film, was detected on ultrasound scan. Moreover, a sonographic examination allowed to establish precisely the localization and size of foreign body. This information was useful during surgical treatment because allowed to limit operative field markedly and to minimize lesion of surrounding tissue, and their existence was confirmed during operation. Owing to results of sonographic examinations it was unnecessary to employ other, supplemental methods of imaging.

The Osgood-Schlatter disease is caused by repeated injuries of tibial tuberosity, which cause damage of the center of ossification and break the bone plate of tibial epiphysis.

Another changes accompanying the Osgood-Schlatter disease are distal inserti-

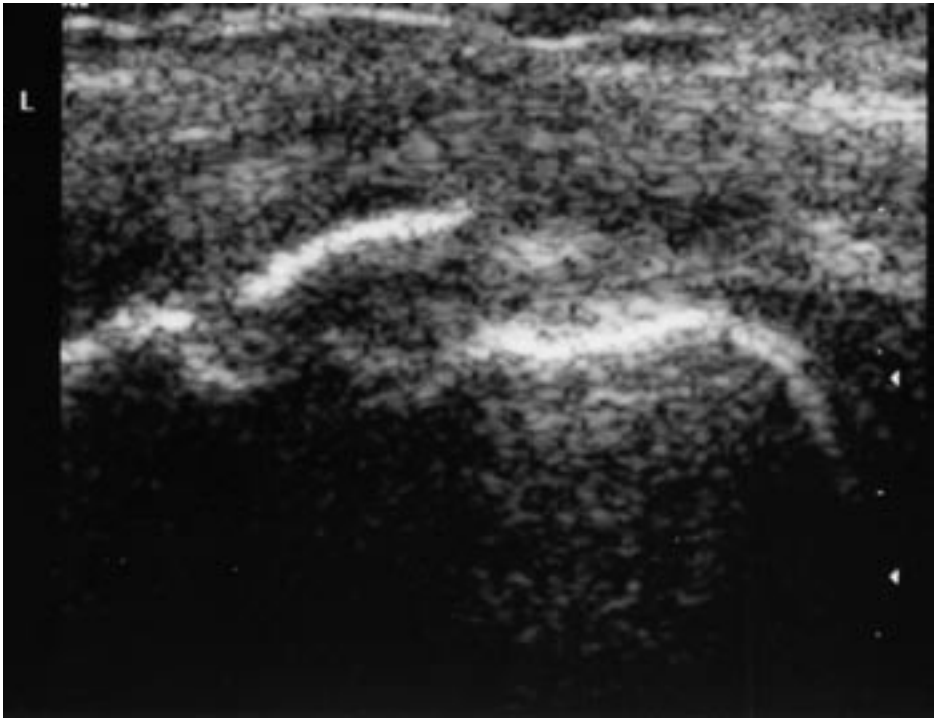


**Fig. 4.** The avulsion fracture of medial collateral ligament

on of patellar ligament tear, intraligamentous calcifications and effusion in deep infrapatellar bursa. The disease occurs in adolescents between 10 and 14 years old and boys are affected three times more often than girls. Typical symptoms include pain and tenderness of the tuberosity, which are exacerbated by physical activity.

In our case a thirteen-year-old boy complaining on the pain of left tuberosity, which had began six months earlier. Standard radiographs did not present any changes in this area. The patient underwent an ultrasound examination which showed all typical sonographic features of the Osgood-Schlatter disease: a fragmentation of the tibial tuberosity, calcification inside the patellar ligament, edema and swelling patellar ligament and effusion within deep infrapatellar bursa. An ultrasound examination makes possible to recognize the Osgood-Schlatter disease in doubtful cases and is important in monitoring of therapeutic effects (**4**).

The third case shows the value of sonography in the evaluation of traumatic patellar dislocation. Ultrasound examination can be helpful in this situation, mainly because of its possibility to demonstrate the presence of osteochondral loose body, which is removed while the lateral edge of patella hits the condyle of femur. A separated frag-

ment can consist only of cartilage tissue, which is not seen in conventional radiogaphy, but could be visualized by ultrasound, if the loose body is present in the part of joint which is approachable for ultrasound examination (**5**).

The confirmation of presence of osteochondral loose body in patients who suffered from traumatic dislocation of patella can shorten the diagnostic algorithm and avoid the MRI examination.

An additional advantage of ultrasound examination in patients who suffered from traumatic patellar dislocation gives the possibility to show other posttraumatic changes in the joint, especially – joint effusion, hemarthrosis, retinaculum disruption (**6, 7**). Ultrasound examination can also visualize incorrect factors which predispose recurrent dislocations of patella like patella alta, lateral patellar subluxation or flattened femoral trochlear groove.

Ruling out the presence of osteochondral loose bodies is an important problem in patients who underwent traumatic patellar dislocation.

In this example the avulsion fracture concerned the femoral attachment of medial collateral ligament. The elevated cortical bone should be differentiated from the presence of ectopic calcifications called the Pellegrini-Stieda disease, but in this patient the period between injury and ultrasound examination was too short and thus the possibility of the second clinical situation was excluded

Finely, it is necessary to mention that ultrasound examination is superior to conventional radiography in the visualization of Salter-Harris type 1 fracture, which can occur in children. In these cases the dislocation of epiphysis can be shown in sonography.

Radiographic diagnostics of musculoskeletal system injuries in children is difficult because of the presence of many cartilaginous parts, which are not visible on conventional x-ray films.

In x-ray examination, pathological changes within muscles, tendos, and ligaments also cannot be visualized (**8**). In these cases, it is necessary to extend the diagnostics and apply other methods such MRI, CT or arthroscopic examination (**9**).

However, this methods are invasive and may be inaccessible in many centers. Therefore, ultrasonographic diagnostics, as noninvasive, inexpensive and commonly used method, ought to be routinely carried out in children after trauma of musculoskeletal system.

In children, with clinical symptoms suggesting post-traumatic injuries of musculoskeletal system and with normal x-ray image, the sonographic examination ought to be obligatory.

## Conclusion

Ultrasonographic examinations are particularly useful in children for visualization of the musculoskeletal changes, which are not visible on conventional x-ray films.

Ultrasonography is especially helpful in detecting and localizing of foreign bodies in joints or soft tissues.

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**REVIEW ARTICLE**

## PRESENT VIEWS ON PATHOGENESIS OF LONG BONE FRACTURE HEALING

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### Summary

Biology of bone healing disturbances is expressed by cellular processes and finds its use in the established standards of orthopedic treatment.

Histomorphogenesis of fracture healing refers to the two principal phases: the first is histochemical one until crystals of hydroxyapatite are absorbed on collagen type one fibers lasting 4 to 6 weeks and second is a phase of piezoelectric stimulation of those crystals after 6–8 weeks from the time of fracture until union. Bone healing disturbances during histomorphogenesis and callus formation may also be due to iatrogenic reasons.

Shortening of some biological processes of fracture union is not possible. Optimalization of time of bone union is elimination of factors that disturb reparative processes during subsequent phases of bone union. Optimal formation of woven bone within the fracture gap is a result of biological and mechanical conditions. The mechanics of fracture treatment should assist biological processes. In cases of bone nonunion probable causing factors should be identified: instability of fixation, coexisting general medical problems, especially concerning hormonal imbalance (thyroid, diabetes), estimation of insufficiencies and supplementation of biologically active calcium and phosphate ions, injections of osteogenic cells by mechanical or biophysical manner or by means of autogenic bone marrow grafting. In cases of structural defects supplementation of bone auto- or allograft may be performed. The eventual plan of operative treatment should include general medical condition of the patient, coexisting illnesses and diseases, age, potential for reconstruction, biologically optimal

qualification, availability of implants and instruments, surgeon experience, patient's profession and future predicted abilities of ambulation. Taking biology of fracture healing into account eases the choice of a proper treatment. The development of tissue engineering and gene therapy increases the number of possibilities of assistance in the treatment of complex problems of long bone healing.

**Keywords:** bone fracture, factors of bone healing

## Introduction

Disturbances of long bone union still cause clinical problems despite of the development in basic and applied research within the subject. Nonunion amount for 5 to 10 % of all fractures (**1**).

Bone healing is a complex process. Disturbances of bone healing result from biological, genetic and mechanical factors.

Biological factors are: fracture localization, bone vascularity, the extent of the injury to soft tissues and wound contamination. Genetic factors come from the incompatibility of bone fracture stabilization with the conditions of bone healing determined by genetic code. Mechanical factors influencing bone healing are: interfragmentary interposition, bone losses, inappropriate fixation, instability and micro movements. Long bone nonunion is influenced by posttraumatic and nontraumatic conditions as well as early and late complications. Healing of fracture may progress at a varied pace. It may progress slowly but leading to fracture consolidation in the time depending on fracture localization, blood supply and the extent of soft tissue injury. Bone union may be compromised by interposition or bone losses leading to nonunion or pseudoarthrosis. Infection challenges all aspects of bone healing. The source of infection may be hematogenous or exogenous, frequently from primarily contaminated high energy open fractures. Infected non-unions involve psychological, economic and social problems and are associated with prolonged morbidity, multiple surgical procedures and extensive antibiotic therapy.

## Aim

The aim of this presentation is to discuss the present pathogenetic opinions regarding biology of long bone healing.

## Histochemistry

Research over histochemical initiators of bone healing and stimulation of maternal cells known also as pluripotential or polyvalent or progenitor, the function of cytokines, prostaglandins and bone morphogenetic proteins (BMP) (**4, 5**).

In the turn of the centuries some types of interleukins and BMP were successfully differentiated and their value to bone healing began to be explored. Some of them were managed to be produced in laboratories. Platelet growth factor is said to be responsible for stimulation of polyvalent cells. It is prepared much easier than previous factors in the form of haemostatic gelatin. Those preparations remain costly, however, which obligates physician to verify indications for its use, to analyze the strategy of orthopedic treatment, keeping in mind the complexity of treatment (**6, 7**).

## Morphogenesis

Stimulation of morphogenesis is possible in respect for osteoblasts progenitors. It was investigated in the turn of the centuries; basic research added a lot of new, clinically important elements. Research work has confirmed the importance of matured cells originating from stem cells and their potential in tissue regeneration (**8**).

Multicenter study in molecular medicine allowed to distinguish three groups of precursor cells found in adults: first group is epiblast-like stem cells able to form cells of all three primary germ layers: ectoderm, mesoderm, and endoderm. The second group of precursor cells is composed of three separate types, each of which is responsible for formation of cells of one only germ layer: ectoderm, mesoderm, and endoderm. The third group of precursor cells which is a progenitor group of cells, is composed of numerous cells found in particular tissues (**9**). Those three groups of precursor cells may be isolated from matured tissues. Those cells can be distinguished by means of their size, the size of cell cultures, gene expression, surface markers, and their potential for differentiation. Summing it up, the authors are discussing the potential of matured precursor cells in tissue rebuilding comparing this process to delivery car for molecular biology (**10**).

The authors state that precursor cells exist within the organism as a cell community dispersed in different tissues.

The three groups of precursor cells derived from adults may be divided basing on their potential for differentiation: epiblast-like stem cells, with tendency for stimulation of tissue vascularization; germ layer lineage stem cells, with tendency for neural cells stimulation; progenitor cells, with potential for repair of articular cartilage, bone tissue, skeletal muscles, revascularization of hypoxemic regions and as tissue grafts in bone marrow transplantation.

Progenitor cells in adults are found in many forms: pluripotential, i.e. tripotential, dipotential, monpotential. Progenitor cells are programmed for particular types of tissues. Monopotential progenitor cells are predisposed for only one type of cells; myoblasts are predisposed for muscles, chondroblasts for cartilage, osteoblasts for bone (**11**).

In practical application it is possible to inject pluripotential cells into circulation e.g. insertion of embryonic cells into compromised tissues, i.e. brain, implantation of bone marrow stromal cells with fibroblast growth factor type 2 and 8, etc. (**12**).

Innovative application of matured stem cells are found in tissue engineering and molecular medicine. At present research scientists are equipped in objective histochemical, immunological, and molecular identification tests of more than 40 distinguishable types of cells, that may be induced to differentiate in cells of particular tissue type (**13**).

Practically there are many sources of pluripotencial cells in hematoma at the site of fracture: germ layer of periosteum, endosteal layer, endomedullary cavities, nutritious canals, Haversian canals, surface of trabecullae and bone marrow.

## Hematoma within the site of fracture

If pluripotential cells are not removed together with hematoma during surgery they will serve as a potential for fracture healing. For biological reasons it becomes important that surgery does not open

the site of fracture in order to prevent from disturbances in healing of long bone fractures (**14**).

Function of integrins in cooperation with osteoblasts: this cooperation results in generation of geometrical structure of extracellular matrix. Extracellular matrix influences the architecture of fracture consolidation. Integrins participate especially in biochemical and physical processes of bone healing. Optimal biological balance between osteoclasts and osteoblasts is important in the process of bone healing. The relation between osteoclasts and calcitonin is important. Activity of osteoclasts depends on the influence of calcitonin which inhibits osteoclasts activity decreasing or totally stopping bone resorption (**15**). In face of a well known fact that resorption within fractured bone ends which goes at pace of 50 micrometers per day and a ten-times slower process of bone tissue rebuilding, which goes at pace of 5 micrometers per day, the inhibitory function of calcitionin deserves its attention and clinical application.

## Piezoelectric stimulation – crystals of hydroxyapatite

Histochemical and morphogenetic processes are the basis for type I collagen fibers formation in the area of bone healing initiation. The presence of those fibers serves as the construction for absorption of crystals of hydroxyapatite. Clinically this process becomes apparent 6–8 weeks after fracture. By means of physical rules crystals have their piezoelectric properties as a result of applied forces: compression and pulling. Alternating compression and pulling forces applied on those crystals influence ion shift, including phosphate and calcium, during bone healing (**16**). Therefore, it is crucial to choose such a method of fracture stabilization within axial skeleton which will enable interfragmentary compression during further treatment. As far as peripheral skeleton is concerned (hanging bones) the method of stabilization should not interfere with stretching forces resulting from the weight of extremity. Compressive forces (axial skeleton) and stretching forces (peripheral skeleton) are genetically conditioned elements stimulating fracture healing. Omitting those elements may be the reason for disturbances in fracture healing to occur. This process is a part of mechanical stimulation of fracture healing.

Biophysical methods of fracture healing stimulation like magnetic field and electrotherapy which base on introduction of electric potential difference in the site of fracture do not exactly simulate the piezoelectric effect or the low of Basset (**17, 18, 19**).

## Callus vascularization

Vascularization of newly formed callus (woven bone) has an enormous influence on a rate and quality of fracture healing (**20**). The progress of fracture healing is conditioned by fracture localization, its type, the presence of primary complications, biological potential of the patient and devascularization of bone fragments (**21**). Among secondary reasons of vascular insufficiency at the site of fracture are: inappropriate reduction, failed fixation, diastases between bone fragments, post surgical infection and thromb-embolic complications. Those reasons of vascular injury can be controlled, therefore, we can prevent them to a certain degree and by doing this we can prevent from distur-

bances of fracture healing to occur. Some of the systemic reasons causing vascular insufficiency compromising fracture healing are: nicotinism, alcoholism, arteriosclerosis, diabetes mellitus, cardiovascular and respiratory insufficiency (**22**).

Substance stimulation of fracture healing is qualitatively individual, it refers to calcium and phosphate balance, hormones and D-group vitamins function, diet optimalization. Those elements of fracture healing stimulation are also interconnected with the quality of callus vascularization (**23**).

## Fracture healing disturbances and posttraumatic haematoma

The presence of pluripotential cells within fracture site and mechanical and biophysical conditions improving bone healing are remarkable biological elements that are to be included in the strategy of treatment of bone healing disturbances. Mechanical conditions refer to endomedullary osteosynthesis with drilling of endomedullary canal, which is in fact endosteal decortication causing hematoma that contains progenitor cells. Biophysical conditions stimulating fracture healing are interfragmentary compression and gravitational pulling which are supposed to lead to cellular metaplasia into osteoblasts (**24, 25, 26**).

Biophysical methods of stimulation of progenitor cells at the fracture site are those that enable hematoma formation: shock waves (lithotripsy) 1500–3000 waves of high energy, pulsatile ultrasounds of low frequency (frequency of 1,5 Mhz, density 30 mW/cm$^2$) (**27, 28, 29**).

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**PROSPECTIVE PAPER**

## "LUBLIN MODIFICATIONS" OF CODIVILLA/TURCO TECHNIQUE IN OPERATIVE TREATMENT OF CONGENITAL CLUBFOOT

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### Abstract

The paper presents the results of surgical treatment of congenital clubfoot in Chair and Department of Pediatric Orthopedics and Rehabilitation of Medical

University in Lublin in years 1975–2005. Authors applied their own modifications of Codivilla/Turco method. In final outcome authors underlined the role of type and range of surgical procedures. They also present the technically optimal procedure: modified skin incision, size of Achilles tendon lengthening, range of capsulotomy. Such modifications in operative technique help to achieve better results in treatment of congenital clubfoot.

**Key words:** clubfoot deformity, operative treatment

## Introduction

Treatment of clubfoot has evolved from minimal surgery and casting technique (Ponseti method) to more extensive surgery. The most popular types of surgical procedures are: according to Evans, Dega, Turco (medial incision), according to Carrroll, Sotirow, Uglov (medial and lateral incision), according to McKay, Crawford, Cincinnatti (circumferential incision). Within the period of 50 years in **Chair and Department of Pediatric Orthopedics and Rehabilitation** in Lublin principles of surgical technique in treatment of congenital clubfoot (from 1955 to 2006) were changed and modified.

## Material

In the years 1970–2005 in our Department 1180 children (1414 feet) were treated surgically with Codivilla/Turco method with the authors own modification. Age of patient extended from 5 to 17 months. Mean age decreased: from 18 months in the 70's to 8 months in 90's. There were 68 % boys (no 803) and 32 % girls (no 377). In years 1970–80 the operated feet had deformity of equinus 90 degree, varus 90 degree and adduction 40–60 degree. These children before surgery were not treated at all or treated insufficiently. In years 1990-2005 the operated feet had deformity of equinus 30–60 degree, varus 20–40 degree and adduction 10–20 degree. In this period the cast treatment was done through 6 to 8 months before the surgery. Material was divided according to type of deformity (according to Dimeglio/Bensahel classification): soft:soft (10 %); soft:stiff (25 %); stiff:soft (40 %); stiff:stiff (15 %).

## Modifications of Codivilla/Turco method

**Skin incision.** In the period from 1955 to 1975 we used straight or "L-like" incision according to Dega (1949) and S-like incision according to Turco (1971). In this period we usually treated children with severe deformations: above 60 degree of equinus, 30-40 degree of varus and 20–30 degree of adduction. In those cases we noticed serious problems with wound closure. Time of wound healing was sometimes longer than 4 or 8 weeks. In results we observed: limit of movement, cicatrix, stiffness or even recurrence of deformity.

Since 1975 in our Department we have been using "W-like" incision (**Fig. 1**). We have now, no problems with wounds' healing. Sometimes good covering of the wound is difficult and in such severe deformation of clubfoot (IV type according to Dimeglio) we use transposition (rotation) of skin flap from shank.

**Technical information about skin transport.** In case of problems with wound closure behind the maleolus medialis we made an additional horizontal inci-

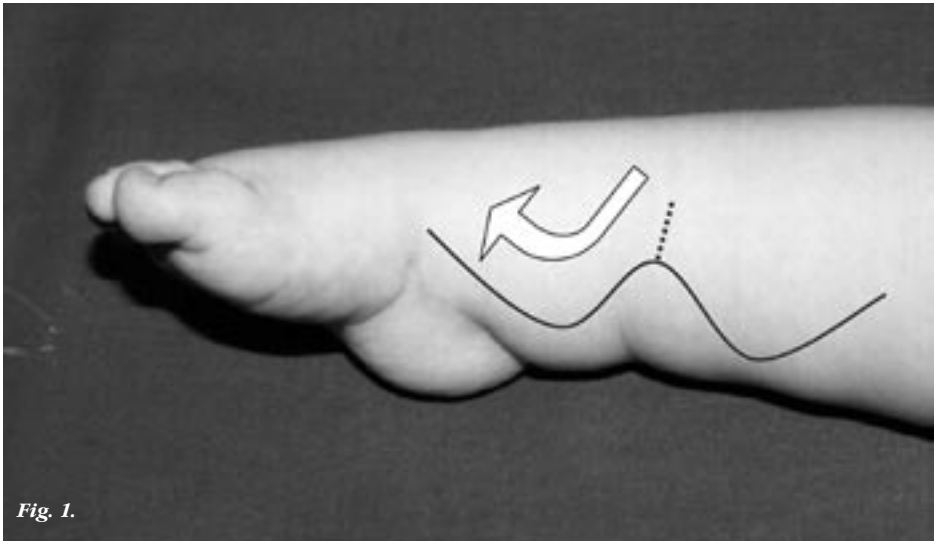

*Fig. 1.*

sion in middle part of "W" incision – in anterior direction. The whole, thick skin flap was carefully separated from shank muscles not to damage the vessels and was transferred with rotation backwards and distally to easily close the wound. The transposition (shifting) was mostly of 1,5 to 3 cm. The healing of this transferred skin flap was correct in 98 % of cases. In 2 % in spite of new wound closure necrosis occurred and healing was "*per secundam intentionem*".

**Size of tendon lengthening.** The size of lengthening of Achilles tendon is very important. Too extensive size of lengthening threatens with development of overcorrected foot. Since 1980 we suture Achilles tendon in equinus position in 5 degree, which protects against development of overcorrecting.

**Range of capsulotomy.** In our Department we care for proper posterior and medial capsulotomy of the ankle joint and subtalar joint. On the lateral side we cut through soft tissues close to tendons of muscles: peroneus brevis and peroneus longus. After surgery the range of dorsiflexion should be no more than 5–10 degree (**Fig. 2**). If these requirement are not fulfilled foot overcorrection and disturbance of blood supply of talus may occur (**4**).

**Muscle imbalance.** Equalization of muscle balance is very important. After correction of equinus, function of both peroneus muscles and tibialis anterior muscle tendon is worse (!) than before operation - since after the correction tendons of these muscles are longer than before (!). Thus, in those cases primary transposition of the tibialis anterior tendon muscle was done (**Fig. 3**).

## Indication for Tibialis anterior (TA) muscle transposition:

a) in primary cases (children in age of 8–10 months) children from the groups: stiff-stiff and stiff-soft; in these cases

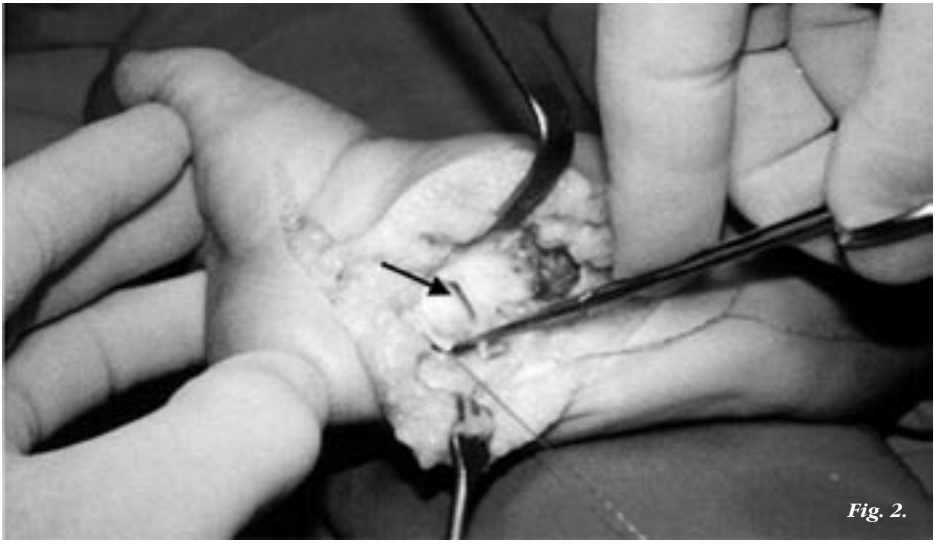

*Fig. 2.*

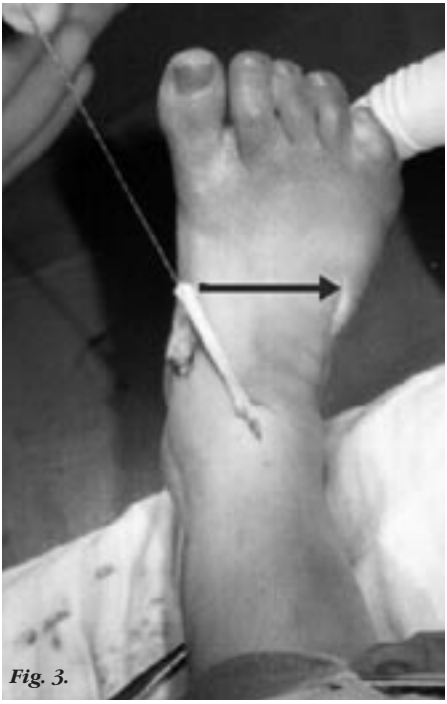

*Fig. 3.*

the varus deformity was dominant and sub-talar joint was with limited movement.

b) in secondary cases (children in age of 3–6 years) in about 25 % of cases of imbalance of pronators and supinators, we made transport of TA muscle to the lateral side of foot, to restore proper balance of muscles.

## Results according to Turco classification

**Period 1975–85.** For follow-up examination 87 patients came forward with 107 clubfeet. Results: excellent – 15 feet (14 %), good – 55 feet (51 %), fair- 11 feet (9,3 %), poor- 28 feet (26 %). 41 feet needed re--operations.

**Period 1986–1995.** 134 feet were assessed in 86 patients. Results: excellent – 28 feet (28 %), good – 50 feet (37 %), fair – 28 feet (21 %) poor – 18 feet (14 %).

**Period 1996-2005.** To follow up examine came 74 patients with 112 clubfeet. Results: excellent – 16 feet (14 %), good – 58 feet (53 %), fair 4 feet (3 %), poor – 34 feet (30 %).

| Result | Outcome of operative treatment according to Codivilla/Turco |
|---|---|
| Excellent | 18.7 % |
| Good | 47 % |
| Sufficient | 11 % |
| Poor | 23.3 % (mostly years 70' & 80') |

## Discussion

A variable percentage of infant clubfeet can not be corrected with cast and/or physiotherapy (**3, 7**). In the 70's the conservative treatment was sufficient at 30 % of clubfeet. Now, 70 % of all clubfeet can be cured with repeated conservative therapy. The remaining 30 % require surgery to complete treatment. It extends from a percutaneous Achilles tendon lengthening to a wide release of medial, posterior and lateral structures, with or without transfer of the anterior tibial muscle tendon (**4**).

Performing the most adequate operation remains "balance on high wire". Deviation on one side threatens the recurrent deformity, on the other side – foot overcorrection.

For the last 30 years, the procedure described by Codivilla and Turco has been generally employed, with some modifications of incision, and amount others of the subtalar release. Some authors used tibiotalar release without subtalar release (**5**).

All patients in Department were treated surgically by Codivilla/Turco method with author's own modification. We underline the very good results and lack of complications during new type of skin incision – W-like incision. We did not notice any problems in skin suture and wound healing. The next very important role was the size of Achilles tendon lengthening – which should be sutured in 5 degree equinus position. It protects against overcorrection and helps to achieve satisfactory results, which corresponds with other author's opinion. The other important factor was the knowledge that too extensive capsulotomy may lead to overcorrection and disturbances in blood supply of the talus (**5**). In some patients we performed elongation of flexor hallucis longus and flexor digitorum longus muscle tendons, which helped to obtain better biomechanical function (**8**). Sometimes we observed that transposition of the tibialis anterior muscle tendon to lateral side was primarily necessary (**10**). It changed acting force direction, resulting in early good function and finally played important role in protection against recurrent deformation.

## Conclusions

1. Range of surgical correction should consider type of deformation, and accompanying additional disturbances like laxity, spasticity (in minimal brain disease – 5 % in our material) or stiffness.
2. "W-like" skin incision and transferring skin flap from tibia enables proper healing.
3. Muscle imbalance between supinators (in plus) and pronators (in minus) groups of foot is the cause of recurrent deformity.
4. Muscle imbalance between flexors and extensors groups after over lengthe-

ning of Achilles tendon and too large capsulotomy is cause of overcorrected foot.

5. Transfer of tibialis anterior tendon to lateral side changes direction of force, results in early good function and protects against recurrent deformation.

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**CASE REPORT**

# POLAND – MOEBIUS SYNDROM AND DISRUPTION SPECTRUM AFFECTING THE FACE AND EXTREMITIES


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## Summary


The author summarizes hitherto assemble experience with the clinical and genetic characteristics of Polands and Moebius syndrome – in the five families. Poland-Moebius syndrome is an overlapping disruption spectrum of inborn defects affecting the face and extremities. The majority of authors are inclined to think that Polands anomaly is part of Moebius syndromic spectrum. Another case-record is devoted to an allied syndrome, hypoglossia-hypodactyly, found in spontaneously aborted fetus. There is, however, a number of other disruption syndromes affecting the face, e.g. the syndrome of hypoglossia-hypodactylia, which greatly resembles Moebius syndrome. The common denominator of all these syndromes and sequences is a disruption sequence on a genetic or non genetic basis. Depending on the site of the vascular disruption anomaly, there are differences in symptomatology, and the

definition of different syndromes is also associated with this problem.

For establishment of a more accurate symptomatology, an irreplaceable place is held by anthropometric examination, for objectifying the asymmetry of the chest the so-called cyrtogram, the chest circumference recorded by means of a wire, is valuable.

Moebius syndrome was described as early as 1888 by the German neurologist P.J.Moebius. Moebius syndrome is a rare condition with a frequency of 1:500 000.

Polands syndrome (sequence) was described in 1841 ast the unilateral absence of the pectoralis major muscle and ipsilateral dermal syndactyly of the hand. The reported frequency is 1:20 000 to 1:30 000. It is maintained that 10 % of all patients with syndactyly have Polands sequence.

From the aspect of genetic counseling, preconception care is always provided to mothers from families with reproductive intentions, as well as ultrasonographic examination of the fetus in areas of assumed acral symptomatology (signaling phenotype). In two families ultrasonography was used for prenatal diagnosis. Invasive prenatal diagnosis by amniocentesis was employed in a family with Moebius syndrome. In these families dermatoglyphs have certain common characteristics, such a tendency towards simple patterns.

In the wider family of one of our patients we detected in a cousin Parkes-Weber-Klippel-Trenaunays syndrome, which may indicate common vascular predisposing factors.

**Key words:** Polands syndrome, Moebius syndrome, vascular disruption sequence, genetics, dermatoglyphs

## Introduction

Poland-Moebius syndrom is an overlapping disruption spectrum of inborn defects affecting the face and extremities. The majority of authors are inclined to think that Polands anomaly is part of Moebius syndrom – spectrum. There is, however, number of other disruption syndromes affecting the face, which greatly resembles Moebius syndrome (hypoglossia – hypodactylia). The common denominator of all these syndromes and sequences is a disruption sequence on agenetic or non genetic basis.

Depending on the site of the vascular disruption anomaly there are differences in symptomatology, and the definition of different syndromes is also associated with this problem (Beer et al. 1996, Bouvet et al. 1978, Fedorov et al. 1997, Matsui et al. 1997).

*Moebius* syndrome was described as early as 1888 by the German neurologist P.J. Moebius. (Moebius, 1888)

At present, just under 300 cases have been described with varying degrees of affliction of the craniofacial area and extremities Moebius syndrome is a rare condition with frequency 1:500 000. (Baraitser, M. 1977, Braye et al. 1996).

Moebius syndrom has a number of synonyms – such as paralysis oculofacialis, agenesis nuclearis, akinesia algera and diplegia facialis congenita – which more or less characterize the disease. A typical features is paralysis of the facial muscles and paralysis of lateral eye **movements to a varying degree, which can be unilateral or bilateral (Henderson et al., 1939,** Sprofkin et al. 1956).

The anatomical correlate of these changes is the congenital absence of the nuc-

lei of cranial disruption sequence of the Moebius type or to primary agenesis of the nuclei of the cranial nerves (Baraitser , 1977, Legum, 1981).

*Poland* syndrome (sequence) was described in 1841 as the unilateral absence of the pectoralis major muscle and ipsilateral dermal syndactyly of the hand. The reported frequency is 1:20 000 – 1:30 000. It is maintained that 10 % of all patients with syndactyly have Polands sequence.

Polands syndrome is, compared with Moebius syndrome, in this sense a more frequent vascular anomaly located in the distal portions of the central nervous systém, extremities and tongue. Poland syndrom anomaly (sequence) is considered a subset of the manifestations of Moebius syndrome and is concurrent with the latter in 15 % of patients. It occurs, however, more frequently separately and can be considered a microform of Moebius syndrome. (Larandaburru et al. 1999).

## Overview

## Moebius syndrom

*Moebius* syndrome affects the VIth and VIIth cranial nerves with manifestations of bilateral central paresis, less frequently with unilateral manifestations (Masaki et al. 1971) Pareses of the IIIrd, Vth, IXth and XIIth cranial nerves are less frequent. Thed first manifestations at a neonatal age are manifested by a mask-like face due tro congenital bilateral damage of the lower motor neuron.

Just as Moebius syndrome and Polands anomaly overlap, the same may happen in the syndrome of hypoglossia-hypodactyly. The common denominator of the two nosological units can be unilateral hypoplasia of the tongue. For Polandś syndrome, on the other hand, athelia and polythelia are typical (Perez-Aznar et al. 1996).

For Moebius syndrome the *orofacial* symptomatology is typical with fasciculations of the tongue, poor speech and pronuncation, and medium or mild hypoplasia of the mandible that calls for orthodontic treatment. (Braye et al. 1996).

For Moebius syndrom a defect of the elastic cartilage of the ear is typical and retraction of the middle portion of the face. Infants with this affliction have difficulties with ingesting food, suffer from hypersalivation, have a small mouth and the function of the soft palate is inadequate.

The *orthopedic* symptomatology of Moebius syndromes involves in 50 % cases defects of the extremities, including hypoplasia and syndactyly in 20 % of cases and deformities of the extremities in 30 %. Les frequent manifestations are clinodactyly, brachydactyly, polydactyly, contractures, dysplasias of the coxae and fibrous ankylosis of the joints – previously of the temporomandibular joint (Hanson et al. 1971, Jorgenson 1971).

Less frequent manifestations are *organ* defects such as congenital heart disease, genitourinary abnormalities and hypogenitalism. *Ophtalmologic* defects include nystagmus, ptosis of eyelids, strabism, epicanthus and corneal ulcerations.

Only in 10–15 % of cases are mental disorders due to *mental* retardation observed. The patients of school age are usually sociable.

*Neurological* manifestations are one of the dominant symptomatologies. The absence of the pectoralis major and minor muscle may be associated with a defect of the m. trapezius, m. quadriceps femoris,

m. serratus and m. semimembranosus and other muscel anomalies.

Supranuclear deaffnes was shown by the method of evoked potentials. Paresis or plegia of the oculomotor nerves is found. The disorder of the XIIth cranial nerve is manifested by an immobile palate. Impaired deglutitons is potentiated by a micromandible. In some children the facial motility improves with advacing age. (Krueger a Fridrich, 1963). Neurological manifestations are one of the dominant symptomatologies.

The heredity can be autosomal dominant with a variable expression, at least in some cases, in relatives microsymptoms in the orofacial area without a reducing acral defect are found.

Despite the fact that autosomal dominant transmission or polyfactorial determination is involved, the majority of patients have mostly sporadic fresh mutations with a restricted reproductive possibility of the carrriers – reduced reproductive fitness.

The gene location of the syndrom is only partially clear, but in another cases not yet clear, however , on the basis of studies of reciprocal translocations and molecular genetic studies it be located with chromosome 1 (1p23) and 13 (13q13). (Ziter et al. 1977, Utermann, G. 2006).

## Poland syndrome

*Poland* syndrome is, compared with Moebius syndrome, a better known, more frequently diagnosed syndrome. In 1980 there were some 300 published cases while 1983 already some 500. The minimal diagnostic criteria of Polands syndrome are unilateral aplasia of the m. pectoralis major and an ipsilateral anomaly or defect of the hand. Facultative manifestations include absence of the nipple of the mammary gland and, in women, inadequate developmentt of the mammary gland.

It has been classified into *three* sub-groups depending on 3 deformities of the hand, described as A, B, C. (Lazjuk et al. 1983) The most frequent (A) is symbrachydactyly associated with brachymesofalangia without oligodactyly – 25 % of these patients have shorter fingers II to IV with thicker medium phalanges.

In group B the distal phalanges of the IInd to IVth finger are absent. Group C suffers from ectrodactyly (cleft) of the hand with an absence of other defects of the carpal bones. This group is rare.

The syndrome include (as main signs) aplasia of the m. pectoralis major and minor. At the same time there is hypoplasia or aplasia of the homolateral thoracic wall. Frequently, flattening of the ipsilateral defect of the chest is observed and rarely an osseous defect of the chest or the absence of fingers. ankylosis of fingers, or facultative hypoplasia of the **forearm** and arm. The biomechanical interpretation of the symptomatology of the chest is that it is deformed due to aplasia of the pectoralis major muscle, and externally the m. serratus anterior is apparent.

Organ disorders are not typical (only supernumerous mammary glands are sometimes present as part of so-called polythelia). Disorder of the major vessels are fairly frequent such as coarctation of the aorta and dextrocardia. Individual hernias of the pulmonary tissue into intercostal spaces are observed as well as inguinal and umbilical hernias.

Goldberg and Mazzei (1977) describe microcephaly and occipital encephalocele, **Rattan et** al. 1996 also a cleft in the area

of the **lumbosacral** spine. Hemivertebrae were also described.

The laterality of findings and the sex ratio are remarkable. A predilections towards laterality is described by various authors. In Polands syndrome mostly boys are affected, according to Lazjuk the ratio is 3:1, while in Moebius syndrome the ratio is 1:1 The results reported by various authors can differ. The majority (45 %) reported in the literature are dextrolatreral. The remainder are partly bilateral or with a crossed symptomatology.

*The etiopathogenesis* is in many respects still obscure. Mostly sporadic cases are involved. A monogenic autosomal dominant transmission has also been described. There exists several syndromological descriptions in siblings and in the offspring of patiens, not only in the later, but also in remote relatives. The etiopatogenesis was studied, e.g. by Goldberg and Mazzei, 1977, Bouvet et al. 1976, David, 1972, and Lazjuk, 1983.

In general a heterogenous etiopathogenesis is assumed, as a rulle local disorders of morphogenesis, while a minority are caused by multifactorial genetically determined stenosis of the subclavian artery (Powell et al., 1993)

*Genetic counseling and consultations, therapy and management:*

**According to** experience, there is no substantially increased empirical risk of re-occurence of the defect in a subsequent empirical risk of re-occurence of the defect in subsequent pregnancy in families with one affected child, if neither of the parents is affected.

Within the framework of genetic consultation in sporadic cases, a detailed examination of the parents of sick children is esential, focused on stigmas such as anomalies of dermatoglyphics and minor shortening of the palms. There may also be micromanifestations of the above symptoms (if they are absent, the prognosis is favorable, if there are minimal manifestations, a risk up to 50 % in the offspring must be foreseen).

Patients with Polands syndrome frequently need plastic surgery of the phenotype. Also, more severe deformities of the thoracic wall call for an operation by a thoracic surgeon. An integral part of therapy is genetic counseling, governed by the general principles outlined above, including counseling such as psychotherapeutic consultations.

## Short communication about case record

The patiens comes from a family with an isolated incidence of Moebius syndrome, age 12 years at the time of the first examination, from the 3rd pregnancy. During mothers **first pregnancy,** his mother had a spontaneous abortion during 10th week and concomitant myomatosis of the uterus, from the second pregnancy a healthy sister of the patient was born. During pregnancy with the proband the mother had excessive weight increments (21 kg during 40th week of pregnancy). The birth weight of the patients was 3200 g/lenght 50 cm.

The defects was assesssed after delivery as paresis of the VII cerebral nerve along with the presence of acral defects, syndactyly of upper right extremity and shortening of the hand, with the ckleft of the 2nd and 3rd finger (**fig. 1**). The left lower extremity is characterized by symbrachydactyly.

From birth his face has the typical appearance of a mask with dropping anguli

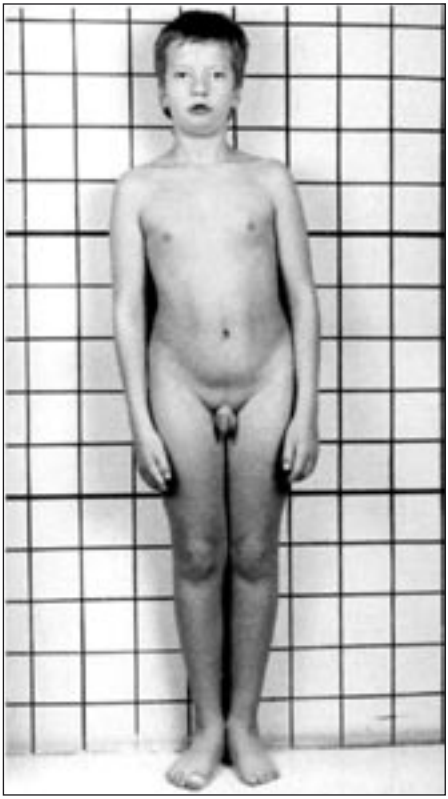

**Fig. 1.** Möbius syndrome, stature at age of 12 yrs, low position of the right nipple, postural scoliosis, symbrachydactyly of the left foot.

oris and ptosis of the eyelids, he cannot close the lips completely, and the mouth is extrtemely small (**fig. 2**). The patient is unable to close the eyelids completely. Occasional spontaneous movedments of the bulb are also observed.

*Important anthropometric parameters at age of 12 years* (**fig. 1**) **right hand shortened by – 3 SD, left planta – 1,8 SD, circumference of right fiorearm – 2,4 SD.** The neurocranium was narrow – 2SD and the bizygomatic distance – 3SD. The left

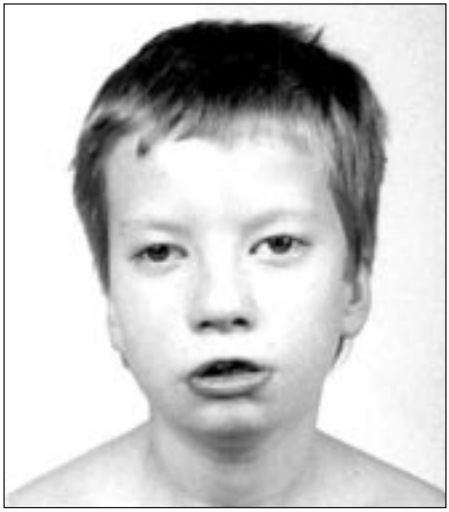

**Fig. 2.** Detail of the face – slight paresis of facial muscels mask-like face, eversion of lower lip (see text).

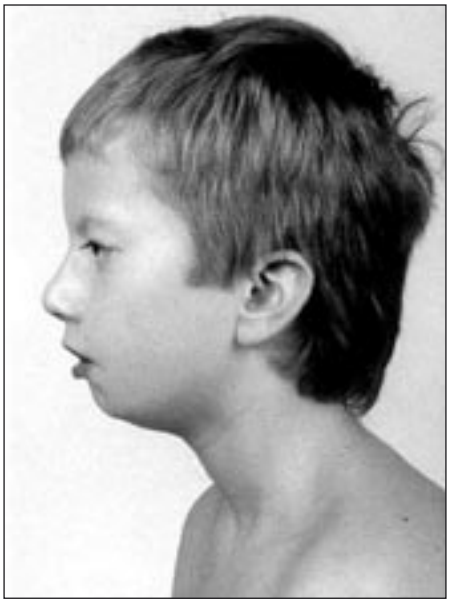

**Fig. 3.** Profile of head and face – low position of ear and same signs as described on figure 2.

lower extremity was reduced by – 1,5 cm.

The chest can be evaluated as asymetric, hypoplasia to aplasia of the pectoral muscles on the right side and associated sinistroconvex scoliosis of the thoracic spine. The nipple on the right side is low.

Intraoral examination at the age of 12 years: marked cariosity of the teeth was revealed and crossed occlusions in the frontal area. The tongue is in central position. The palatinal arches are symmetrical, the motility of soft palate is restricted. The are of (TM) joints without pathological phenomena. The patients speech is faint and mumbling, While rinsing his mouth during dental examinations, he supports his lower lip to prevent water escaping from his mouth. The patients attends elementary school with average progress.

The described typical appearance of the face is due to the central paresis of the VIth and VIIth cranial nerves, and as a result to impaired innervation of the m. rectus bulbi temporalis and the mimic muscles. The face noted masklike face, eversion of the lower lip.

The impaired motility of the soft palate, which is the main cause of the impaired speech, also indicate an affliction of the IX$^{th}$ cranial nerve, the ramus styloglossus of which innervates the muscle bearing the same name, as well as the m. glossopalatinus and levator veli palatini. The impaired speech is due to the weakend mimic muscles. The increased cariosity of teeth is explained by poor hygiene of oral cavity. The small oral cavity makes perfect cleaning of teeth difficult, while the poor mobility of the deformed hands contribuutes to the inadequate brushing of the teeth. The weakend mimic muscles have a reduced role in self cleansing.

## Discussion and conclusion

The combination of Moebius and Polands syndrome is derscribed in the literature rather rarely. We found this association in one of our female patients. At least in some of the cases a disruption variability is involved, as mentioned. Also the contralateral involvement of the extremities in this syndrome is of interest. Minguella and Cabrera (1998) presented a report on a large number 38 patients from Spain – 28 boys and 10 girls. There was a slight predominance of leftsided afflictions 20/18. This is relatively new finding as compared with the formerly reported lateral predilection.

The authors paid attention to anomalies of the hand and divided the patients, based on clinical and radiological findings, into five groups – without syndactyly, with syndactyly and brachymesophalangy (hypoplasia or aplasia of the middle phalanx), type 3 with syndactyly including the thumb, type 4 – longitudinal deficiency of some fingers or the radius and type 5 – with a transversal absence of the skeleton of the hand.

The most frequent anomaly is aplasia of middle phalanx of the fingres (15 cases) or its hypoplasia (another 15 cases). We also observed this finding in one of our 5 case records. A cleft hand was observed in two patients with manifestations pf Moebius syndrom but not in isolated Polands syndrome.

Anesthesiologists draw attention to possible complications of anesthesia in Polands syndrome caused by paradoxical breathing due to deformity of the chest wall. In this syndrome emphysematous bullae were also described (Sethuraman et al. 1988). There are also rteports that syndactyly in Polands syndrome is usually more serious from a functional aspect than

other types of syndactyly, even surgery was successful (Kramer et al. 1998).

Dysontogenetic changes predispose in general also to oncogenic lability of the organism. Evidence of this effect was provided by the work of Athale and Warrier describing Wilms tumor in patients with Polands syndrome (1998). The position is complicated also by the fact that patients with Polands syndrome are more liable to develop leukemia, and this must be taken into account during radiation treatment and chemotherapy, therapeutic modifications are necessary. As to other tumors in Polands syndrome, neuroblastomas have been described (Caksen et al. 1997).

Polands syndrome also holds an important place within the framework of morphological anomalies of the chest and mammary gland in girls. (Grolleau et al. 1997). It is thus an important field for plastic surgery. Reconstructive surgery is focused on the thoracic wall, including implants and mammary glands making use of silicone (Gatti , 1997, Hodginson 1997, Longaker et al. 1997).

As a disorder of mesodermal tissues is involved, the finding of hemocoagulation disorders is not surprising. The vascular etiology is suggested by the joint finding of a defect atrial septum and Poland-Moebius syndrome described by Matsui et al. 1997. Bouvet mentions atypical features of the blood supply of the afflicted extremity by plethysmography. Hypoplasia if the subclavian artery is assumed – on the same side at the affect extremity.

Obviously, this is not so in all patients but, on the other hand, a common disruption sequence „subclavian artery supply disruption sequence“ (SASDS) is assumed, which explains the common pathogenesis not only of Polands and Moebius syndrome but also of Klippel – Feils syndrome (sequence), isolated terminal acral defects and Sprengels anomaly. The critical period of this abnormal pathogenesis (dysontogenesis) is the six week of gestation. Explanations for the vascular theory obviously does not apply to cases with a contralateral symptomatology.

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**PROSPECTIVE ARTICLE**

# PREDICTION OF THE LEG SHORTENING AND INDICATION OF ORTHOPAEDIC TREATMENT AT CHILDREN

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## Summary

Lower limb length inequality is a consequence of many congenital and acquired musculoskeletal affections. The authors summarize their experience with prediction methods of the lower extremity lengths discrepancies, choice of the most suitable treatment method and timing of the surgery. The treatment strategy and the choice of the most suitable method depend on prediction of the final shortening. Based on groundwork of Moseley and Shapiro, the authors developed their own prediction methods. It combines auxology, anthropometry and teleroentgenograms. The authors have experience with more than 100 patients with lower extremity discrepancy, in 60 of them surgical treatment was carried out. The abbreviations higher than 5–6 cm are treated by lengthening. Epiphyseodesis is an appropriate method for the equalization of shortenings 2–5 cm as shown on case reports. The most accurate timing of epiphyseodesis could be developed using remaining growth charts by Anderson – Green. The authors present results of prediction and comprehensive treatment in patients with fibular hemimelia, proximal femoral focal deficiency, angiodysplasia Klippel-Treunaunay syndrome, hemihyperplasia (EMG or Beckwith-Wiedemann syndrome) who achieved adult height.

**Key words:** Lower extremity length discrepancy, prediction, auxology, remaining growth

## Introduction

Lower limb length discrepancy is a consequence of many congenital and acquired musculoskeletal affections. The most common congenital affections are congenital limb defects (e.g. proximal femoral focal deficiency – PFFD, congenital short femur, fibular hemimelia or complex femur-fibula-ulna – FFU), hyperplasia or hypoplasia of one leg, consequence of hemihyperplasia (Beckwith-Wiedemann syndrome), angiodysplasia Klippel Trenaunay, etc. Inequalities of lower limbs can be a symptom of some osteochondrodysplasias (e.g. Chondrodysplasia punctata Conradi-Hünermann type, Dysplasia epiphysealis hemimelica, Multiple cartilaginous exostoses, Enchondromatosis Ollier type, Fibrous dysplasia McCune-Albright type, neurofibromatosis, etc.). Acquired discrepancies of limbs are consequence of neonatal septic arthritis, Perthes‘ disease, injury of epiphyseal plates by trauma, oncological treatment, inflammation (juvenile chronic arthritis), irradiation, long-lasting immobilization as well neurogenic origin – e.g. hemiparetic forms of cerebral palsy.

On the basis of experience with more than 100 patients with above mentioned diagnoses (approximately in 60 of them surgical treatment was carried out), the authors summarize their experience with

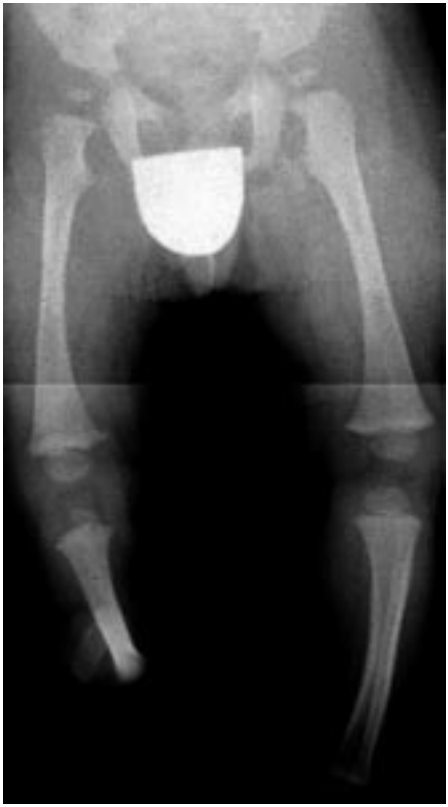


**Fig. 1.** X- ray of lower extremities of 6 months old boy with fibular hemimelia l. dx., type 2 according to Achtermann and Kalamchi, rudimentary foot and impaired distal tibial epiphyseal plate. Predicted discrepancy of legs was 25–30 cm.

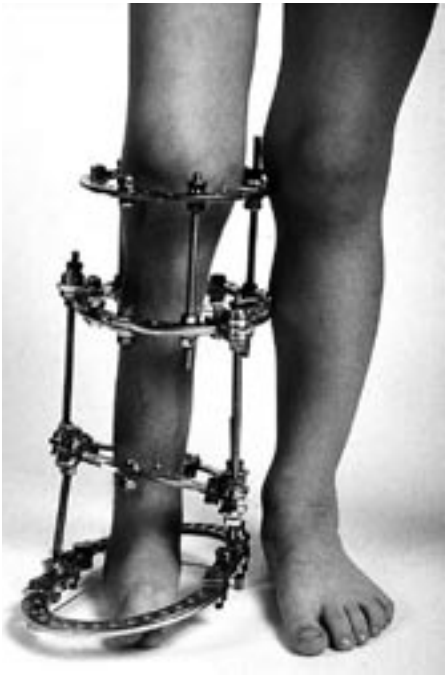


**Fig 2.** Step by step lengthening of the right shank (combination of callotaxis of distal part of tibia and epiphyseal distraction of proximal epiphysis) in 4–5 years of age.

prediction methods of the lower extremity length discrepancies, choice of the most suitable treatment method and timing of the surgery.

The treatment strategy and the choice of the most suitable method depend on prediction of the final shortening. That is why the prediction methods were worked out on the basis of literature statements and of those of our experience (**3, 10, 11**). The abbreviation less than 2 cm is treated by insoles and/or orthopaedic shoes. Shortenings 2–5 cm can be treated by corrective shortening osteotomy after the completion of the growth. In growth period (usually at the end of growth spurt), epiphyseodesis in the knee region is the most suitable and safe surgical method. We prefer this method due to its low invasivity. This method of treatment needs long- term observation of child growth velocity because of timing of epiphyseodesis is the most important and depends on experience of orthopaedic surgeon and anthropologist.

Shortening among 4.0–20.0 cm are indicated to lengthening by the method according to Ilizarov. Severe discrepancies are solute by combination of lengthening with epiphyseodesis. Shortening more than 20.0 cm is more appropriate for prosthetic (or orthoprosthetic) fittings.

Our prediction methods are based on auxological (**4, 5, 6**), radiological (**7**) and orthopedic literature **(8, 3**)) and have been revised according to our results. The most important author who was engaged in length inequality problematic is F. Shapiro (**2001, 8**)). On the basis of more than 800 patients he stated that most but not all length discrepancies increase continuously with growth. Developmental patterns depend on the nature of the conditions causing the inequality and time of their occurrence. He divided the developmental patterns into 5 types. The developmental pattern in the individual patient is specified on the basis of diagnosis and revised and refined during long-term follow-up.

One of the most common patterns is type I: upward slope, where the ratio between the affected and non-affected segments remains constant. This information enables us prediction of the final shortening on the basis of teleroentgenograms (X-rays of legs in standing) before treatment and on the basis of auxological data (**3, 4, 5, 7, 8, 10**). This pattern is characteristic for PFFD, Enchondromatosis Ollier type, for most cases of FFU complex and for hemiparetic forms of cerebral palsy.

In most cases of hemihypertrophy (hemihyperplasia), neurofibromatosis and congenital short femur shortening develops according to type I, but sometimes we found also type II: upward slope – deceleration pattern or type III: upward slope – plateau. Regular monitoring during the growth period is the essential tool of prediction specifying.

On the other hand in Perthes disease, juvenile chronic arthritis and after femur fracture the most common is type III: upward slope – plateau pattern. In some cases (especially in Perthes disease) shortening can increase in puberty (type IV: upward slope- plateau-upward) or equalization can be reached (type V: upward-plateau-downward that is common in juvenile chronic arthritis).

## Case reports

From the group of 33 patients with femoral and fibular deficiencies 3 cases who already reached adult height were chosen for demonstration. Authors present the prediction method, surgery treatment and its results. **Case 1** is a boy with femur hypoplasia and FFU syndrome. The final discrepancy was in accordance with our prediction and performed prolongation. **Case 2** shows a girl with bilateral FFU syndrome. Three lengthening procedures about 5 cm resulted in equalization of predicted 15 cm discrepancy. **Case 3** suffered from fibular hemimelia, type 2 according to Achtermann and Kalamchi with rudimentary foot and impaired distal tibial plate – **Fig. 1.** Predicted discrepancy was 25–30 cm. These severe cases of fibular hemimelia are usually indicated to Syme amputation and prosthetic fitting but parents did not agree with this standard orthopaedic method. That is why we decided for reconstructive surgical treatment. In the 1st year the excision of fibular fibrocartilaginous anlage was performed and later step by step lengthening of the right shank was carried out in 4–5 year of age – **Fig 2.** Combination of callotaxis of

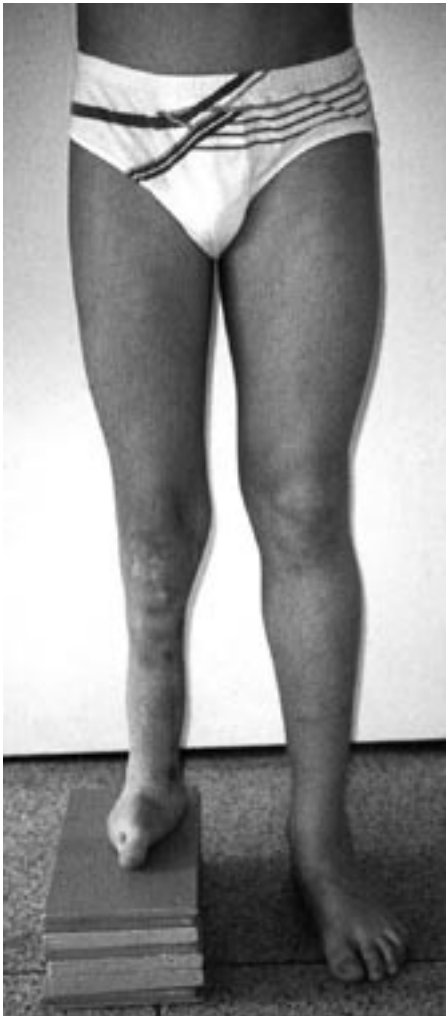


**Fig. 3.** Shortening of the right shank and foot reached 10 cm when the boy was 13 years old.

distal part of tibia and epiphyseal distraction of proximal epiphysis was indicated. In next years of life the boy was fitted with orthopaedic shoes. Next stage of lengthening was indicated at the age of 13 years when shortening of the right shank and

*Fig. 4*

foot reached 10 cm – **Fig. 3.** We decided for proximal epiphyseal distraction of the right tibia. With respect to growth spurt and very good tolerance from the side of patient the step by step lengthening of the right tibia on 18 cm was carried out – **Fig. 4, 5.** Later a corrective wedge osteotomy of the right proximal tibia was performed. At **Fig. 6 and 7** you see the young man in 19 years of age. The legs are equal, flexion of the right knee is restricted to 100°. Both stereotype of gait and concentration of pressure strains under the sole are normal.

In case of complications (e.g. fractures of bone regenerates, inflammation about

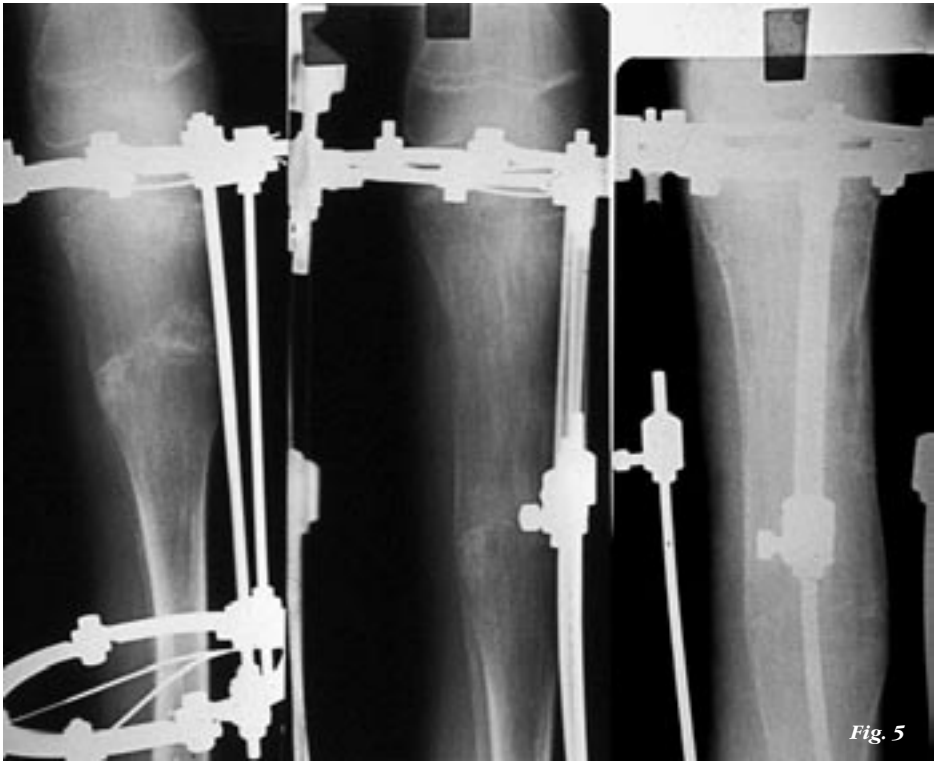



**Fig. 4, 5.** Montage of external fixator on the right leg – unilateral Prospon advice was joint to Ilizarov apparatus to prevent dislocation and contracture of the knee joint. X-rays (**Fig. 5**) document excellent mineralization of distraction gap during proximal epiphyseal distraction of tibia. With respect to growth spurt and very good tolerance from the side of patient the step by step lengthening of the right tibia on 18 cm could be carried out and by this way the equality of legs was reached. Later a corrective wedge osteotomy of the proximal right tibia was performed to correct some degree of valgosity.

Kirschner wires, Sudeck's algoneurodystrophy), the benefit of prolongation can be lower than the real length of bone tissue regenerate. We often observe lower growth velocity of elongated long bones in next years. From the point of timing the lengthening should be carried out in period of growth inactivity. Our next task will be complex evaluation of the results (and complications) of lengthening procedure from the view of biological, biomechanical and other aspects.

In last years epiphyseodesis was performed in 20 patients. Very good result of epiphyseodesis is shown at **case 4.** A girl with hemihyperplasia (Beckwith-Wiedemann syndrome, EMG syndrome) had shortening of the right leg 3.5 cm at the beginning of puberty – **Fig. 8 a, b.** The predicted lower limb discrepancy


*Fig. 6*

**Fig. 6 and 7** document the patient in 19 years. The legs are equal, flexion of the right knee is restricted to 100°.

was 4.0–4.5 cm. Epiphyseodesis was made at the bone age 12.8 years (according to Greulich-Pyle (GP) and Tanner-White 3 (TW3 RUS)). At the age of 16 years the final shortening was 0.5–1.0 cm – **Fig. 9a, b.** On the **case 5** a girl with angiodysplasia Klippel Trenaunay is demonstrated.


*Fig. 7*

Predicted discrepancy of legs was 5.5 cm. The authors illustrate the process of shortening prediction and good result of epiphyseodesis.

## Conclusion

The exact assessment of bone age (according to Greulich-Pyle (**2**) and Tanner-White (**9**)) and sexual maturity is the main prerequisite for the right timing of epiphyseodesis. Proper timing of epiphyseodesis is necessary condition for successful equalization of legs. In previous study (**11**) we proved that remaining growth charts by Anderson and Green (**1**) are the most suitable method for timing of epiphyseodesis. According to experience of both authors the growth charts by Pritchett (**6**) are not suitable for Czech population.

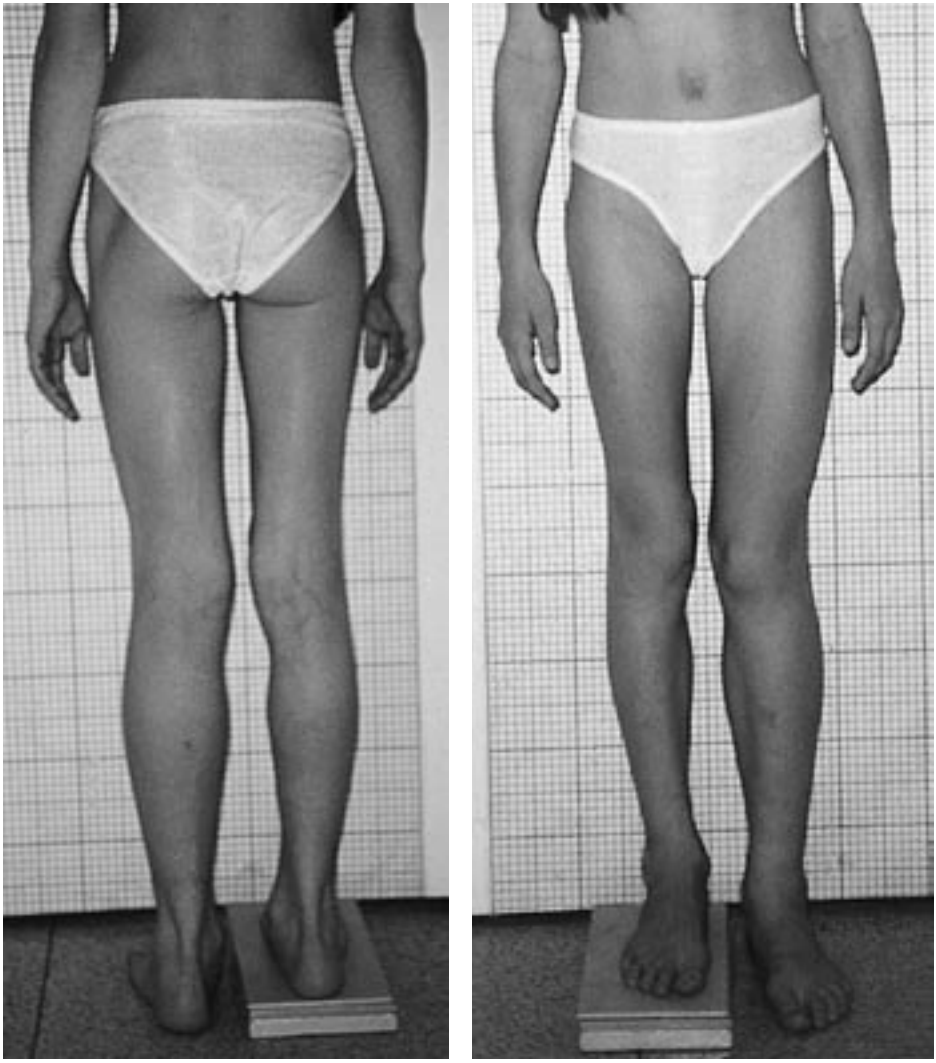
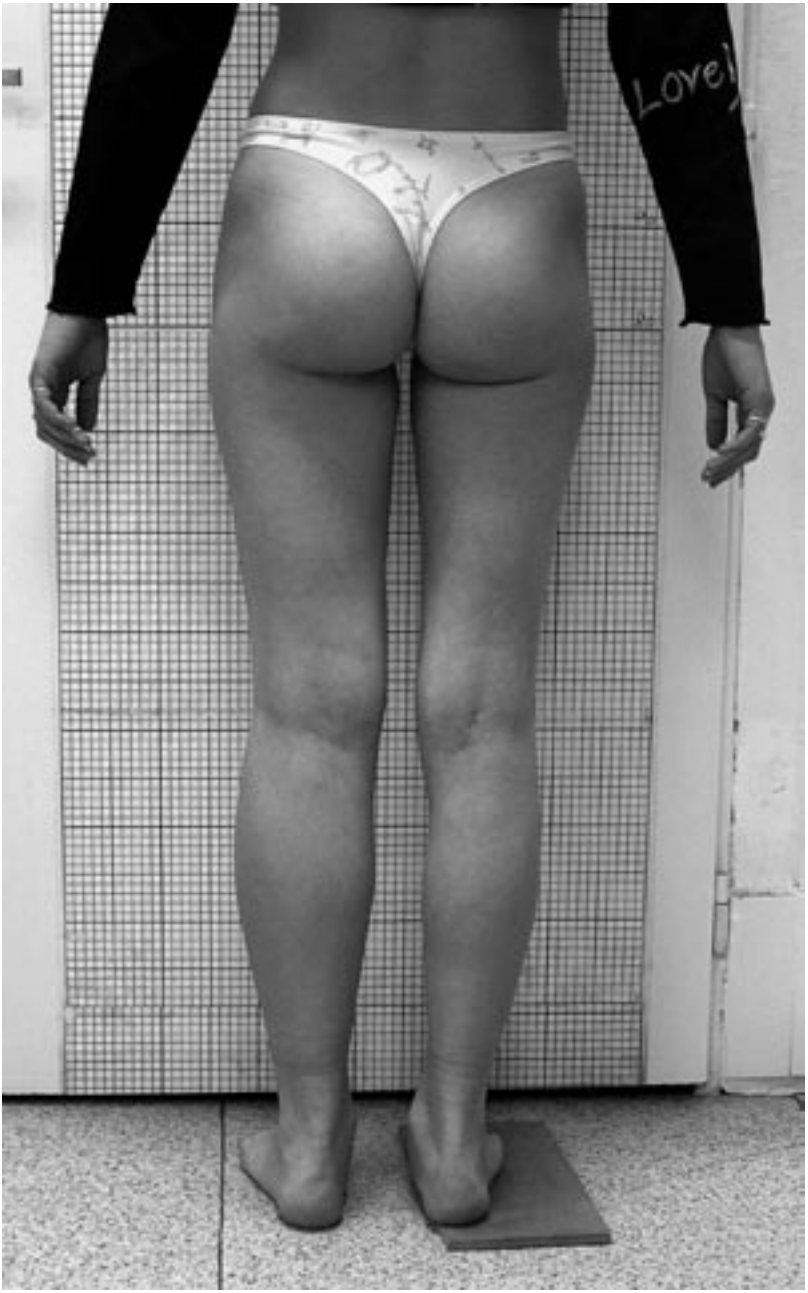


**Fig. 8 a, b.** Stature of a girl with hemihyperplasia (Beckwith-Wiedemann syndrome, EMG syndrome) in the age 12.5 years. Shortening of the right leg was 3.5 cm. The predicted discrepancy of legs was 4.0–4.5 cm.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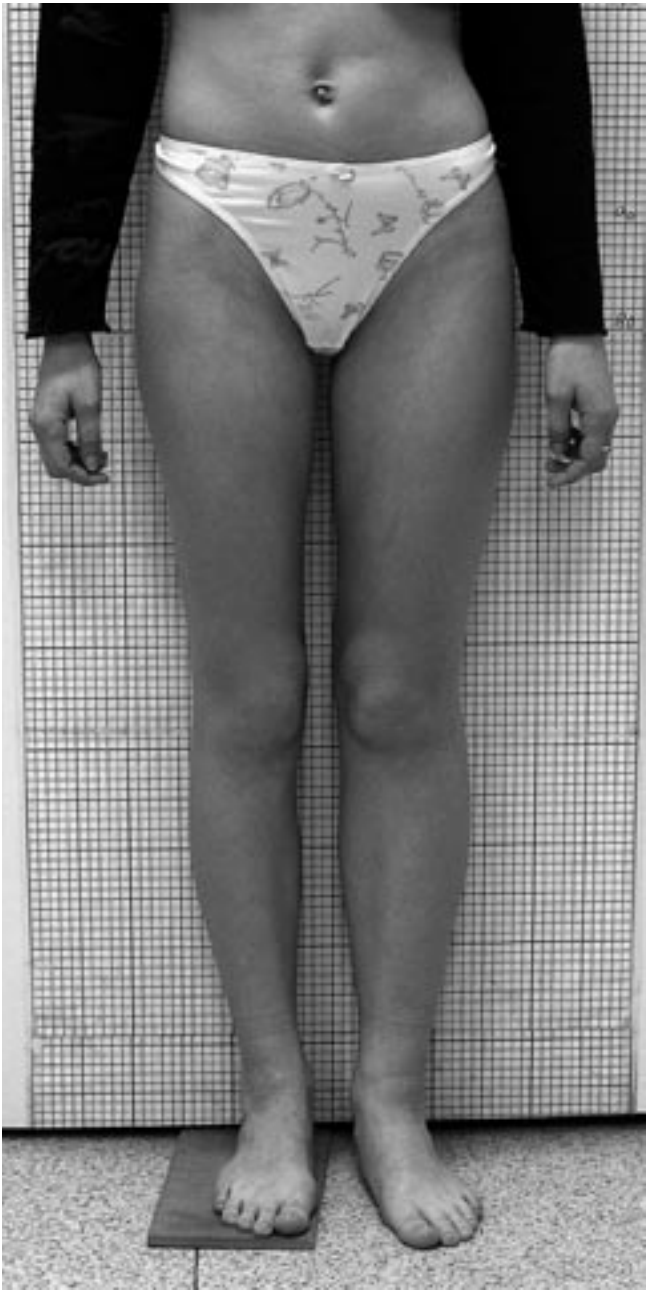

**Fig. 9a, b.** The patient in 16 years – 3 years after epihyseodesis – the shortening was 0.5–1.0 cm. Very good result of surgery.

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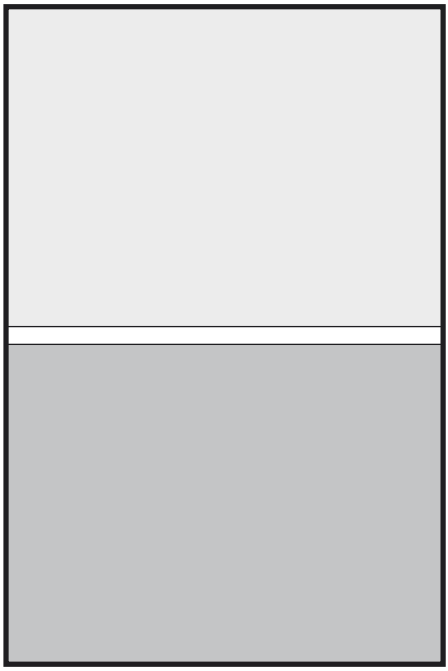
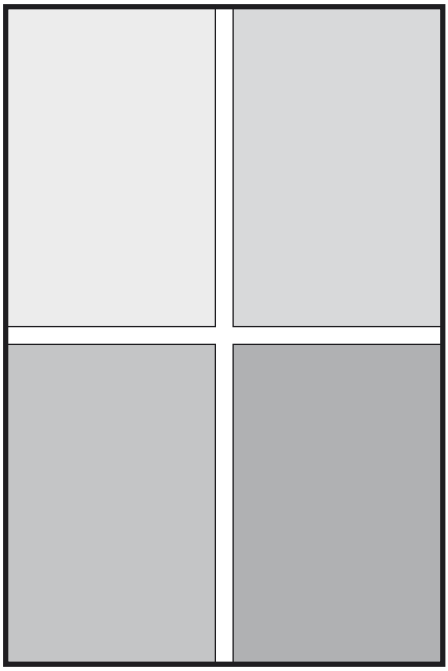




Při opakovaném vydání a uveřejnění více inzerátů možnost slevy po dohodě s vydavatelem

# Osteologická Akademie ČLS JEP Zlín

**Obecně prospěšná společnost**

Osteologická Akademie ČLS JEP Zlín (OAZ) je společnost při předsednictvu ČLS JEP, jejímž cílem je koordinace výuky metabolických onemocnění skeletu ve spolupráci s ostatními pracovními skupinami ČLS a SMOSu. Pro tento účel vytváří klastrové skupiny pro jednotlivé problematiky.

Díky stávajícím praktickým možnostem (největší skupiny pacientů v ČR, klinické ambulance, laboratorní a instrumentální diagnostika) vytváří integrální potenciál, který dává podmínky pro dosažení nejvyšší možné produktivity a efektivnosti lékařského a vědeckého poznání v oblasti metabolických onemocnění skeletu s postupnou aplikací na pacienta.

Tato klastrová organizace bude mít následující přínosy:

**1. Pro pacienty**

Budou obeznámeni s optimálním algoritmem prevence, resp. léčby onemocnění. Na základě těchto znalostí mohou spolupracovat s ošetřujícím týmem.

**2. Pro lékaře**

Bude místem a institucí, kde bude výše zmíněný cíl koordinován. Možnost měnlivosti složení clusteru bude dávat prostor pro nestandardní postupy, které budou ověřeny na modelech i v praxi. Výstupem budou konkrétní závěry jako podklad pro praktický postup směrem k pacientovi, k Ministerstvu zdravotnictví ČR a zdravotním pojišťovnám. Budou vytvářeny optimalizované modely léčby, které budou díky klastrovému uspořádání obsahovat závěry i z jiných oborů (např. dietetologie, gastroenterologie, onkologie, etc.).

Tento koncept umožnuje dosažení optimalizace medicínské i ekonomické.

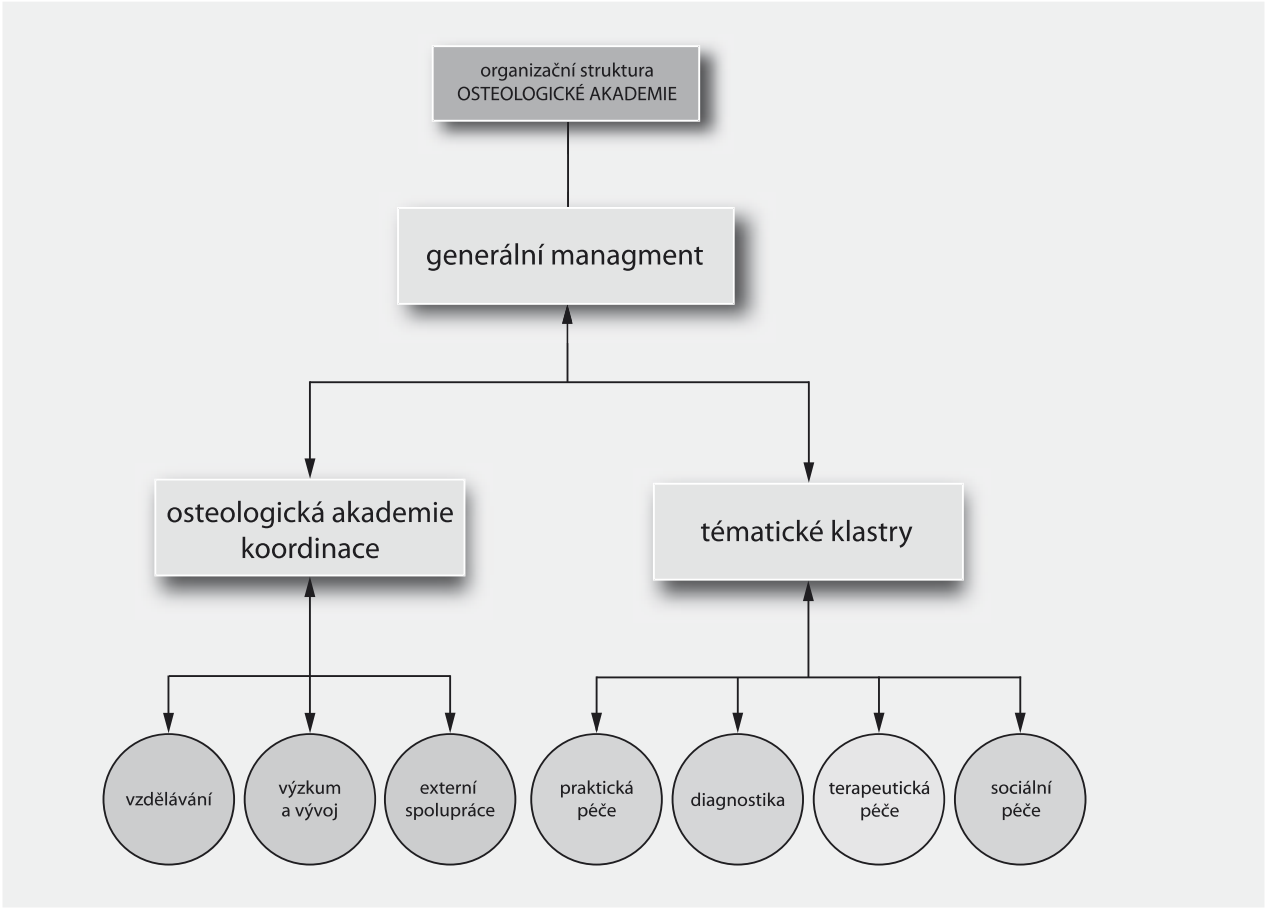
**3. Pro ČSL JEP**

Společnost může na modelu klastrové optimalizace ověřit řešení složitých mezioborových medicínských problematik – vyplývá to z organizační struktury klastru, její variability a rychlé schopnosti reakce v daném medicínském oboru.

**4. Pro ČR**

Vznikne optimalizovaná organizační struktura pro mezioborové problematiky, kde se prolíná rovina akademická, rovina soukromé medicíny, státní zprávy a pojišťoven. Organizační schéma managementu umožní maximálně optimalizovanou reakci na změny v diagnostice, prevenci a léčbě v ČR pro danou oblast medicíny. Může posloužit jako model pružného řešení složitých medicínských mezioborových problémů bez ekonomických ztrát.

Organizační struktura i ekonomická pravidla Osteologické Akademie Zlín budou plně v souladu s praktiky ČSL JEP a jejím etickým kodexem.


organizační struktura
OSTEOLOGICKÉ AKADEMIE
generální managment
osteologická akademie
koordinace
tématické klastry
vzdělávání
výzkum
a vývoj
externí
spolupráce
praktická
péče
diagnostika
terapeutická
péče
sociální
péče

# Osteologic Academy of the Czech Medical Society of Jan Evangelista Purkyne in Zlin

**Non-profit organization**

The Osteologic Academy of Zlin (OAZ) established by the Czech Medical Society of Jan Evangelista Purkyne (CMS JEP) is an institution reporting to the board of directors of CMS JEP. The goal of OAZ is to coordinate the education in the field of metabolic skeletal diseases and collaborate with other departments of the Czech Medical Society and the Society for Metabolic Skeletal Diseases. OAZ creates clusters to address several problem areas.

Having the greatest number of patients in the Czech Republic, outpatient departments, laboratories, and instrumental diagnostics OAZ represents an integral potential enabling to achieve significant advancements resulting in a higher effectiveness and productivity of applied medical and scientific knowledge in the field of the metabolic skeletal diseases.

This cluster organization brings the following benefits:

**1. For patients**

They will learn correct procedures and optimal ways of preventive care, i.e., the treatment of their diseases. This improves patient's cooperation with their physicians.

**2. For physicians**

OAZ will coordinate the aforementioned goals. The possibility to adjust the composition of the cluster will allow for non-standard procedures that will be verified using models and in practice. Specific conclusions will serve as a basis for practical treatments of patients and for collaboration with the Ministry of Health of the Czech Republic and insurance companies. Optimized methods of treatment will be created and due to the cluster organization they will also include considerations and recommendations from other related specializations (for instance from dietetology, gastroenterology, oncology, etc.).

Such approach enables not only a medical but also overall economic effectiveness.

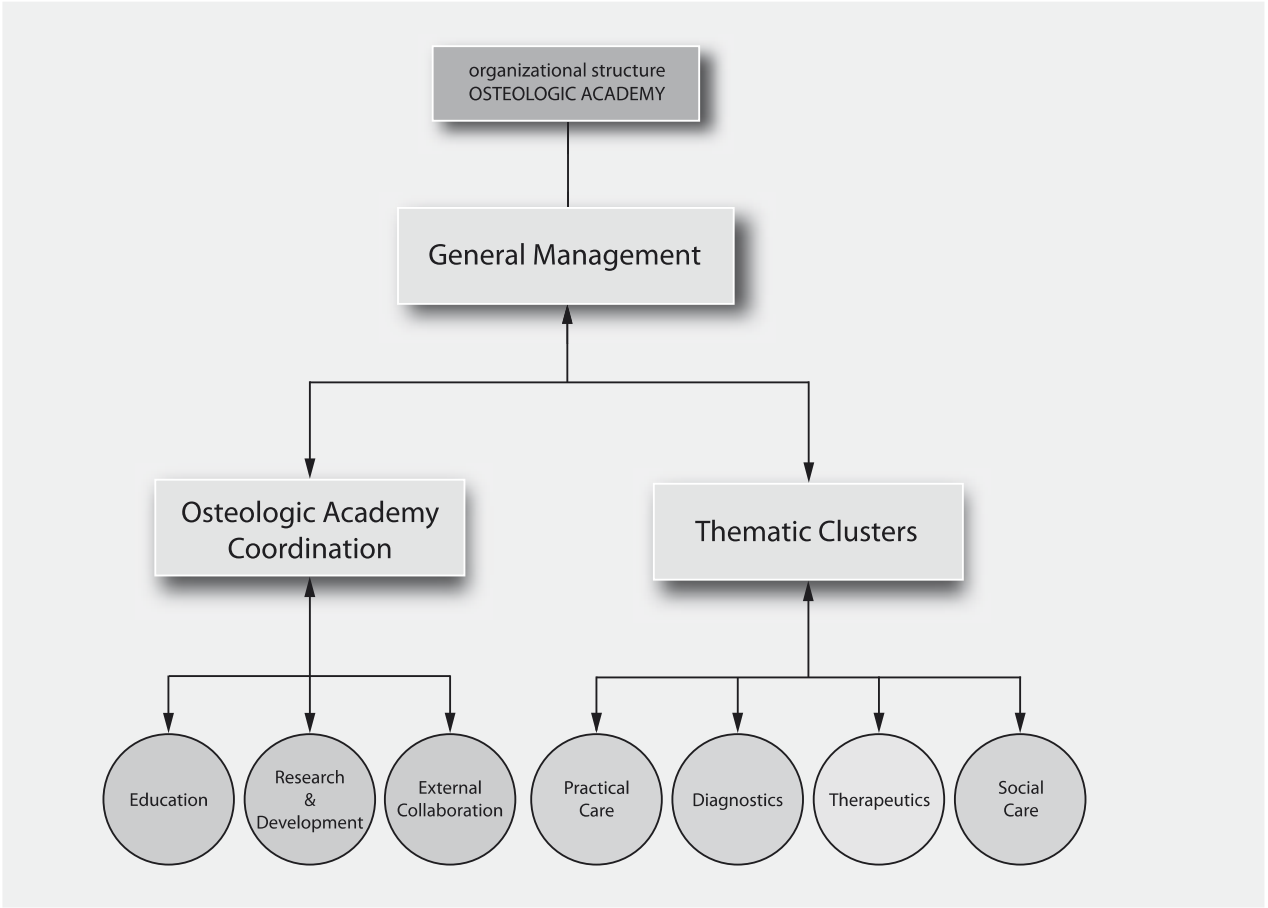
**3. For CMS JEP**

The organization will be able to validate solutions for complex interdisciplinary medical issues using the cluster optimization model. Cluster organization structure has a build-in flexibility and ability to react quickly in a given medical field.

**4. For the Czech Republic**

An effective organizational structure will be created to address interdisciplinary matters where the academic level, the private medical sector, the nation sector, and the insurance companies will cooperate and influence each other. Such management provides for optimized reaction to changes in diagnostics and recommended preventive care in the Czech Republic. This approach may serve as a model for a solution of really complex interdisciplinary medical issues while preventing economic losses.

The organization structure and the economic rules of the Osteologic Academy of Zlin will fully comply with regulations of CMS JEP and its ethical code.


organizational structure
OSTEOLOGIC ACADEMY
General Management
Osteologic Academy
Coordination
Thematic Clusters
Education
Research
&
Development
External
Collaboration
Practical
Care
Diagnostics
Therapeutics
Social
Care

# The Utah Paradigm of Skeletal Physiology

## Volume I
## Bone and Bones and Associated Problems

**Chapter 1:** Introduction and format. Preamble; scientific, clinical and communication challenges; self test; fundamental idea; the book's format

**Chapter 2.** Wolff's law and related matters. The past, present and future.

**Chapter 3:** Bone modeling. Bone architecture, mechanical functions and effects, gains, conservation, IO-biomechanics. The three-way rule. Bone development, adaptations and functions; baseline conditions; strain histories; modeling drifts; macromodeling, minimodeling, micromodeling; mechanical usage effects; role of muscle strength; six principal adaptations; special features; a modeling analogy; modeling functions and rules; set points; chondral modeling barrier; overshoot; other matters.

**Chapter 4:** Bone remodeling. Architecture, turnover, mechanical functions and effects. Bone "mass" and strength, conservation, losses, IO-biomechanics. The four-way rule. Observations; the remodeling BMU; rho; marrow mediator mechanism; remodeling space; cement lines; mechanical effects; thresholds; disuse patterns; a remodeling analogy; remodeling functions and rules; feedback loops; transient and steady states; set points; adaptational slowdown; other matters.

**Chapter 5:** The skeleton's mechanical usage windows. Mechanical usage, strains, microdamage; biologic mechanisms; yardstick; disuse, adapted, mild overload and pathologic windows; bone strength; strength-safety factor; fatigue life; thresholds; variability; chronic states.

**Chapter 6:** Illustrative clinical problems (that involve the IO-biomechanics of bone). Design of endoprostheses; drugs, genetics and set points; stress fractures; osteomalacias and fatigue fractures; skeletal including bone pain; autocorrection of malunions; aseptic necrosis of the femoral head; homeostasis; the mechanostat; definitions of physiologic osteopenias and true osteoporoses; restoring bone to osteopenic skeletons; some clinical situations explained by the Utah paradigm; humoral and genetic effects; minimizing fatigue damage; brief recapitulation.

## Volume II
## Fibrous (Collagenous) Tissues, Cartilage, Synovial Joints and Associated Problems

**Chapter 1:** Introduction. Three lives of skeletons; basic functions; the Utah paradigm's index and organization functions; a self test; the book's organization.

**Chapter 2:** Some tissue-level fibrous (collagenous) tissue physiology. tendon, ligament, fascia, connective tissue, io-biomechanics. Observations; major functions; general IO-biomechanical relation; scar and mature tissue; baseline conditions; mechanical usage history; end, muscle and creep growth in length; diametric modeling; set points; the fibron; tension transfer fan-out; disuse-mode remodeling; turnover; creep; clinical implications; regional acceleratory phenomenon; microdamage detection, repair, balance and pain; overuse syndromes; mechanical usage rules; ultimate control; adaptational slowdown or lag; other things.

**Chapter 3:** Some tissue-level cartilage physiology. Growth plates, joint cartilage, limb alignment, ligament-tendon attachments, io-biomechanics. General functions; growth-modeling distinction; baseline conditions; loading history; chondral growth-force response curve; joint alignment; limb length errors; ball and socket ankle; hip dysplasia; epiphyseal height; joint surface congruence; perichondral ring roles; attachments of tendon, ligament and fascia to bone; joint size; Sharpey's fibers; cartilage-bone relationship; other things.

**Chapter 4:** Synovial joints: some principles of design, function, architecture and IO-biomechanics. Observations; primary purpose of joints; plan of synovial joints; baseline conditions; building materials; design considerations; momentarily loaded area; the MESm criterion; loading history; diametric growth; joint shape, curvature and congruence; stiffness adaptations; menisci; alignment adaptations; other matters; cartilage and bone maintenance; adaptational slowdown or lag;

**Chapter 5:** Some io-biomechanical causes of arthroses. (osteoarthritis, degenerative joint disease). Definition of arthroses; aging and time; obesity; joint malalignments; subchondral bone stiffness; role of a meniscus; high spots; underloading; true overloads; relative underloads; maintenance failures; mechanical usage windows; comments; lead times (sigmas); set points.

**Chapter 6:** Illustrative clinical problems. (that involve the IO-biomechanics of fibrous tissue and cartilage). Pes planus; obesity and arthroses; sports medicine; arachnodactyly; chondrodystrophies; trigger finger; osteochondritis dissecans; hallux rigidus; slipped capital femoral epiphysis; lateral patellar facet syndrome; long bone torsions; the paradigm's domain; relative roles of mechanical and nonmechanical influences; more on joint alignment; roles of humoral agents and genes; pseudarthrosis of the tibia; the frozen shoulder syndrome; ligament healing; more on fatigue damage; more about the mechanostats; recapitulation; conclusion.

**HAROLD M. FROST**,
**M.D., D.Sc. (Hon)**

*Surgeon, Clinician, Investigator,*
*Theoretician and Teacher*

The International Society of Musculoskeletal and Neuronal Interactions was most fortunate to be able to publish these 2 volumes entitled **"The Utah Paradigm of Skeletal Physiology"** by Harold M. Frost, a founding member and Honorary President of the Society at the time of his passing. **Harold M. Frost**, M.D., D.Sc.(Hon) called himself a Feisty, Eccentric, Old Dinosaur (F.E.O.D.). He was that except not old in mind. He never lost his lust for science. He was a smart orthopaedic surgeon with hobby of "corresponding and jawboning with clinical and research scientists regarding skeletal science, medicine and surgery".

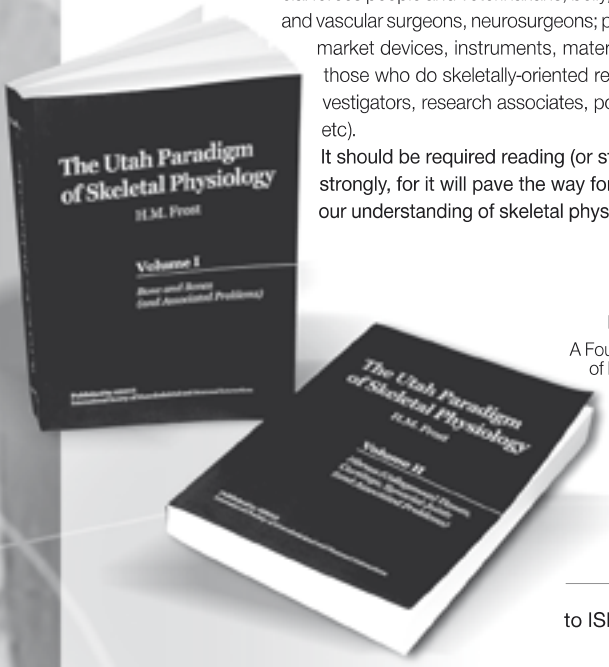
In these two volumes entitled **"The Utah Paradigm of Skeletal Physiology"**, **"Vol I: Bone and Bones and Associated Problems"** and **Vol II: Fibrous (Collagenous) Tissues, Cartilage, Synovial Joints and Associated Problems"**, Harold has documented his current understanding of skeletal physiology from his half century journey. The volumes should be a concern to all who manage, study and/or teach skeletal and related problems in clinical, laboratory, classroom and other settings and all who support the involved research and education: anatomists, anthropologists, biochemists, biomechanicians, cardiologists, coaches, trainers, dentists, endocrinologists, engineers, experimentalists, gastroenterologists, urologists, histologists, metabolic bone disease authorities, materials scientists, neurologists, nurses, orthodontists, oral surgeons, orthopaedic surgeons, their residents and professors, paleontologists, pathologists (experimental, forensic and clinical), pediatricians, phychiatrists, physical therapists, physiologists, pediatric and plastic surgeons, pulmonary disease specialists, radiologists, rehabilitation specialists, rheumatologists, space and sports medicine people, special forces people and veterinarians, belly, chest, ear-nose-throat, ophthalmologic and vascular surgeons, neurosurgeons; plus those who design, manufacture and market devices, instruments, materials and supplies for such people; and those who do skeletally-oriented research in the above areas (principal investigators, research associates, post-doctoral fellows, graduate students, etc).

It should be required reading (or study) for those above. I recommend it strongly, for it will pave the way for all to fill in the blanks and accelerate our understanding of skeletal physiology.

**Webster S. S. Jee, Ph.D.**
Professor of Anatomy

Co-Editor-in Chief of the Journal of
Musculoskeletal and Neuronal Interactions

A Founding Member of the International Society
of Musculoskeletal and Neuronal Interactions

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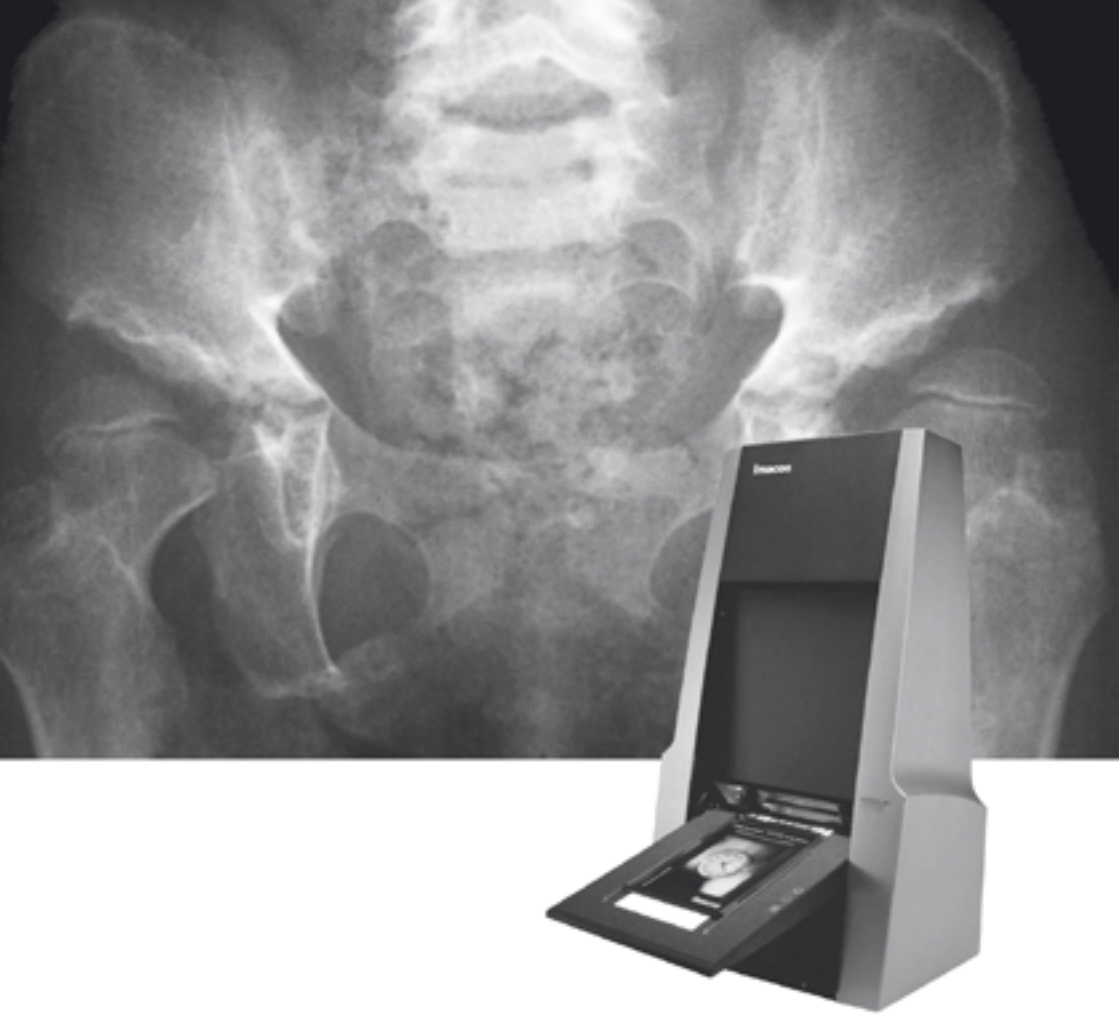

Skenování odrazových předloh a reálných předmětů do formátu 305 × 457 mm a tloušťky 20 mm, transparentních předloh (pozitivů i negativů) do formátu 250 × 457 mm na skenerech Heidelberg TOPAZ II a Imacon FLEXTIGHT 848. Retuš a barevné úpravy skenovaných i dodaných obrazů na monitoru EIZO CG220. Sazba, zalomení textu a následné operace. Grafické návrhy. Zprostředkování digitálního i ofsetového tisku.

S
G R
sazba
grafika
retuš

Pavel Lorenc, Podkovářská 6, 190 00 Praha 9
tel./fax 266 036 067, e-mail: pavel.lorenc@volny.cz

# Ortopedická protetika Praha s.r.o.

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- Zhotovení všech individuálních ortopedických pomůcek (protézy HK a DK, končetinové a trupové ortézy, měkké bandáže, ortopedickou obuv, ortopedické vložky apod.

**provozní doba:**
**po** 7.30–17.00; **út–čt** 7.30–16.00; **pá** 7.30–15.00

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Metro C stanice Chodov, dále autobus č. 118 stanice Dědinova – budova MEDICENTRUM

Partner všech zdravotních pojišťoven v ČR


BNV/08.06/044/0360

# První bisfosfonát, na který stačí myslet pouze jednou měsíčně

JEDNOU MĚSÍČNĚ
Bonviva
Acidum ibandronicum
Je jenom jedna

**Držitel registračního rozhodnutí:** Roche Registration Ltd., Welwyn Garden City, Velká Británie. **Registrační čísla:** EU/1/03/265/003, EU/1/03/265/004. **Účinná látka:** Acidum ibandronicum 150 mg ut Natrii ibandronas monohydricus 168,75 mg. **Indikace:** Léčba osteoporózy u žen po menopauze se zvýšeným rizikem zlomenin. Bylo prokázáno snížení rizika zlomenin obratlů, účinnost na zlomeniny krčku proximálního femuru nebyla stanovena. **Kontraindikace:** Hypokalcémie, hypersenzitivita na ibandronovou kyselinu nebo na kteroukoli pomocnou látku. **Dávkování a způsob podávání:** K perorálnímu podání. Doporučená dávka je jedna 150mg tableta jednou měsíčně. Tableta by měla být užita každý měsíc ve stejný kalendářní den. **Zvláštní upozornění:** Před zahájením léčby přípravkem musí být upravena hypokalcémie. Stejně by měly být léčeny jiné poruchy kostního a minerálního metabolismu. U všech pacientek je důležitý dostatečný příjem vápníku a vitaminu D. Užívání bisfosfonátů může být spojeno s dysfagií, vznikem ezofagitidy a jícnových nebo žaludečních vředů. Zvýšená opatrnost při současném užívání s NSAIDS. Přípravek není doporučován u pacientek s hodnotami clearance kreatininu pod 30 ml/min. U některých pacientek (většinou onkologických) léčených bisfosfonáty byla hlášena osteonekróza čelisti. **Těhotenství a laktace:** Přípravek by neměl být podáván během těhotenství a kojení. **Klinicky významné interakce:** *Interakce s potravou:* Pacientky by měly před užitím přípravku dodržet celonoční lačnění (alespoň 6 hodin) a neměly by přijímat potravu další hodinu po požití přípravku. *Interakce s ostatními léčivými přípravky:* Pacientky by neměly užít jiný perorální léčivý přípravek alespoň 6 hodin před a 1 hodinu po užití přípravku. Nebyly prokázány interakce s tamoxifenem nebo hormonální substituční terapií (estrogeny). Při podání přípravku současně s H2 blokátory nebo jinými aktivními látkami zvyšujícími pH žaludku je nutná úprava dávkování. **Klinicky významné nežádoucí účinky:** Časté nežádoucí účinky léčivého přípravku (> 1/100, 1/10), které byly zaznamenány ve studiích a jejichž výskyt může dle zkoušejících souviset s léčbou přípravkem: dyspepsie, nausea, bolest břicha, průjem, nadýmání, gastroezofageální reflux, bolest hlavy, únava, myalgie, artralgie, vyrážka. **Dostupná balení:** Bonviva 150 mg 1 nebo 3 tablety. **Podmínky pro uchovávání:** Žádné zvláštní podmínky uchovávání. **Poslední revize textu:** 13. 10. 2006.

gsk GlaxoSmithKline

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Roche