

SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (Ph.D.)

TOPICAL TREATMENT OF OSTEOPOROSIS BY
IONTOPHORESIS USING
CALCIUM- AND PHOSPHATE-DONATING
MICROPARTICLES

by Izabella Ilona Gomez MD

Supervisor: Zoltán Szekanecz MD, PhD, DSc



UNIVERSITY OF DEBRECEN
DOCTORAL SCHOOL OF CLINICAL MEDICINE
DEBRECEN, 2013

Topical treatment of osteoporosis by iontophoresis using calcium- and phosphate-donating microparticles

By Izabella Ilona Gomez, MD

Supervisor: Prof. Zoltán Szekanecz, MD, PhD, DSc

Doctoral School of Clinical Medicine, University of Debrecen

Head of the **Examination Committee:** András Berta, MD, PhD, DSc

Members of the Examination Committee: László Módis, MD, PhD, DSc

István Takács, MD, PhD

The Examination takes place at the Library of the Ophthalmology Clinic, Medical and Health Science Center, University of Debrecen, on 25th June, 2013.

Head of the **Defense Committee:** András Berta, MD, PhD, DSc

Reviewers: Péter Lakatos, MD, PhD, DSc

Sándor Szántó, MD, PhD

Members of the Defense Committee: László Módis, MD, PhD, DSc

István Takács, MD, PhD

The PhD Defense takes place at the Lecture Hall of Building 'A', Institute for Internal Medicine, Medical and Health Science Center, University of Debrecen, on 25th June, 2013.

1. Introduction and background

Bone is a living tissue that not only protects internal organs but also serves as a mineral reservoir. It consists mainly of elastic fibers of proteins and crystals of hydroxyapatite. The bone also contains cells including some that controls the bone remodeling. The imbalance of resorption and formation results osteoporosis characterized by low bone density and a deterioration of microarchitecture that reduces strength leading to increased fragility. Osteoporosis affects a great percentage of the population, more than 750 million citizens worldwide.

Several systemically administered antiporotic drugs are available. However, local therapeutic modalities may also be useful. Some studies suggest that “calcium ionostasis” and iontophoresis of certain compounds including hormones may have beneficial effects on osteoporosis, fracture healing or Complex Regional Pain Syndrome.

In the 1990's *in vitro* optimization of calcium iontophoresis was carried out by Pap et al. For more effective ion donation, two specific lattice layer was developed. This has been accompanied by the development of a three-electrode iontophoretic device what enables the independent migration of cations and anions.

2. Research aims

The aim of my Ph.D. study was to perform first in the world *in vitro* investigations, *in vivo* and *postmortem* experiments for the setting of the novel calcium and phosphate iontophoresis treatment, for the detection and clarification of its effects and efficacy on animal bones.

The main issue to be answered was whether the novel iontophoretic apparatus and ion donor microparticles specifically developed for this purpose are applicable for calcium and phosphate transdermal delivery into bone.

My specific aims were as follows:

- To investigate *in vitro* whether calcium and phosphate ions are delivered into the target porcine bone by the novel iontophoresis and to determine the extent of calcium and phosphate concentration changes in bone
- To investigate *in vivo* the effects of the novel iontophoresis in terms of changes in bone density, biomechanical parameters and calcium and phosphate ion concentration of rat bone
- To compare the *in vivo* effects of the novel iontophoresis with estrogen supplementation on osteoporotic rat bones

3. Materials and methods

3.1. Materials for simultaneous calcium and phosphate IOP

3.1.1. Calcium and phosphate donating molecules

Specially modified, toxic-free calcium-bentonite based molecule and synthetically produced hydrotalcite was used for our study as calcium and phosphate sources, respectively.

3.1.2. Iontophoretic apparatus

A novel three-electrode iontophoretic apparatus, constructed to meet safety requirements, was utilized for each experiment. This instrument is adequate for simultaneous iontophoresis (IOP) as it forms two separate circuits with the help of zero electrode.

3.2. Elemental analyses

Wet digestion was completed by microwave assisted digestion of the samples weighting 0,5 g each. Calcium concentration was analyzed using flame AA spectrometer while phosphate concentration was detected by an UV/Vis spectrophotometer.

3.3. *In vitro* experiments of calcium and phosphate IOP (Study 1)

3.3.1. Tissue specimens

For *in vitro* studies pig back limbs were used. Samples were divided into 3-3 groups each containing 6 samples in preliminary

(Groups A-C) and 15 samples in the extended experiments (Groups 1-3). Group A and 1 served as controls, Group B and 2 were treated with iontophoretic current only and Group C and 3 were treated with IOP. After treatment, samples of skin and muscle from both electrode sides and of bone were taken.

3.3.2. IOP treatment

The anode and the cathode containing ion donors on their surface were applied onto the skin at two sides. The time of treatment was 40 minutes. 9.5 mA current intensity was applied in both circuit.

3.4. In vivo experiments (Study 2 and Study 3)

3.4.1. Experimental animals and surgical procedures

Experiments were carried out on Sprague-Dawley female rats randomly assigned into the groups. Animals were anesthetized with ketamine-xylazine combination (25/75mg/kg i.p.). The ovaries were removed as described in the literature. Sham-operated (SH) animals underwent median laparotomy only.

3.4.2. Quantitative ultrasound bone densitometry (QUS)

Changes in Amplitude-Dependent Speed of Sound (AD-SoS) were detected at the left tibia by DBM-Sonic 1200 densitometer.

3.4.3. IOP treatments

The IOP was started at 8 months of age (day 0) and repeated 4

times on days 2, 4, 11 and 18. Time of treatment was 30 minutes and 9 mA current was used in both circuits.

3.4.4. Experimental design

3.4.4.1. Preliminary *in vivo* study on rats (Study 2)

IOP was carried out on sham-operated and ovariectomized rats (Group 1, SH+IOP and Group 2, OVX+IOP). Group 3 and 4 served as controls. IOP was performed on the left tibia under anesthesia.

3.4.4.2. Extended *in vivo* experiments on rats (Study 3)

Twelve-week-old animals were assigned into SH (n=16) and OVX rats (n=24). Animals in Group 1 and 2 were SH or OVX and were not subjected to any further interventions (SH, n=10 and OVX, n=6). Other rats were subjected to serial local IOP (Group 3, Sham+IOP, n=6 and Group 4, OVX+IOP, n=6). E2 was initiated in another subgroup (Group 5, OVX+E2, n=6). In some of the rats E2 was combined with IOP (Group 6, OVX+E2+IOP, n=6). At the end of the experiments tibias were ejected *postmortem*.

3.4.5. Estrogen therapy

In order to compare the effects of iontophoresis with estrogen therapy, 5 times a week 17 β -estradiol (sc. 20 μ g/kg) was administered into OVX+E2 and OVX+E2+IOP groups. The OVX and OVX+IOP animals received vehicle treatment only.

3.4.6. Biomechanical tests

Bones were break-tested in a three-point bending procedure utilizing Instron4302 servohydraulic instrument. Maximal load and stiffness was detected as described in the literature.

3.5. Statistical analysis

All data are expressed as means $\pm$ standard error of the mean (SEM). Data analysis was performed with SigmaStat and SPSS 17.0 software. Differences between groups were analyzed by two-way or two-way repeated measures ANOVA. Differences between p values <0.05 were considered statistically significant.

4. Results

4.1. Study 1: *In vitro* experiments of simultaneous calcium and phosphate IOP on porcine tissues

4.1.1. Calcium elemental analysis

When iontophoretic current was only applied, the calcium content of the muscle on the anode side decreased (Group B: $608,74 \pm 8,6 \mu\text{g/g}$; Group 2: $235.7 \pm 66.7 \mu\text{g/g}$) compared to controls (Group A: $811,15 \pm 33,34 \mu\text{g/g}$; Group 1: $278.2 \pm 33.2 \mu\text{g/g}$) ($p<0.05$). No significant differences were found in other tissues. When donors were applied, calcium concentration of skin and bone significantly

increased (Group C: $mc_{\text{skin anode}}: 895,5 \pm 18,7 \mu\text{g/g}$ and $mc_{\text{bone}}: 205334,8 \pm 7842,28 \mu\text{g/g}$; Group 3: $mc_{\text{skin anode}}: 793.0 \pm 108.6 \mu\text{g/g}$ and $mc_{\text{bone}}: 207628 \pm 16198 \mu\text{g/g}$) in comparison to controls (Group A: $mc_{\text{skin anode}}: 278,26 \pm 33,19 \mu\text{g/g}$ and $mc_{\text{bone}}: 112367,4 \pm 2374 \mu\text{g/g}$; Group 1: $mc_{\text{skin anode}}: 319.7 \pm 38.9 \mu\text{g/g}$ and $mc_{\text{bone}}: 124560 \pm 15551 \mu\text{g/g}$) ($p < 0.05$).

4.1.2. Phosphate elemental analysis

Applying the IOP instrument itself had no significant effects on phosphate contents. When using donor molecules, the phosphate content of the skin and the bone significantly increased (Group C, $mc_{\text{skin anode}}: 407,89 \pm 32,27 \mu\text{g/g}$; $mc_{\text{skin cathode}}: 557,92 \pm 32,02 \mu\text{g/g}$; $mc_{\text{bone}}: 227025,33 \pm 13446,33 \mu\text{g/g}$; Group 3, $mc_{\text{skin anode}}: 392.7 \pm 33.2 \mu\text{g/g}$; $mc_{\text{skin cathode}}: 662.4 \pm 32.2 \mu\text{g/g}$ $mc_{\text{bone}}: 244342 \pm 13798 \mu\text{g/g}$) in comparison to controls (Group A, $mc_{\text{skin anode}}: 298,61 \pm 46,66 \mu\text{g/g}$; $mc_{\text{skin cathode}}: 329,9 \pm 92,55 \mu\text{g/g}$; $mc_{\text{bone}}: 185248,63 \pm 1417,33 \mu\text{g/g}$; Group 1, $mc_{\text{skin anode}}: 287.0 \pm 28.5 \mu\text{g/g}$; $mc_{\text{skin cathode}}: 342.4 \pm 20.4 \mu\text{g/g}$; $mc_{\text{bone}}: 195321 \pm 10393 \mu\text{g/g}$) ($p < 0.05$).

4.2. Study 2: Preliminary *in vivo* studies on rats

AD-SoS loss was detected in OVX rats compared to SH animals (Group 1: $1869.8 \pm 39.93 \text{ m/s}$; Group 3: $1826.83 \pm 47.93 \text{ m/s}$ vs. Group 2: $1649.3 \pm 29.94 \text{ m/s}$; Group 4: $1673.6 \pm 15.07 \text{ m/s}$)

($p < 0.05$). As a result of IOP, the AD-SoS values were increased in comparison to controls (Group 1: 2057.15 ± 41.37 m/s; Group 3: 1866 ± 23.21 m/s; Group 2: 1958.8 ± 60.69 m/s; Group 4: 1730 ± 23.37 m/s) ($p < 0.05$). This favorable effect was persistent (at day 150: Group 1: 2047 ± 14.94 m/s; Group 3: 1947.6 ± 47.93 m/s; Group 2: 1967.8 ± 28.15 m/s; Group 4: 1775.4 ± 21.97 m/s) ($p < 0.05$).

4.3. Study 3: Extended *in vivo* experiments on rats in order to determine the effects of iontophoresis versus estrogen therapy

4.3.1. Bone density changes

21 weeks after ovariectomy, a decrease in AD-SoS value was detected (Sham: 1887.9 ± 10.23 m/s; Sham+IOP: 1897.5 ± 31.40 m/s; vs. OVX: 1681.1 ± 16.26 m/s; OVX+IOP: 1673.6 ± 12.30 m/s; OVX+E2: 1695.1 ± 20.21 m/s; OVX+E2+IOP: 1634.0 ± 19.94 m/s).

Serial IOP caused sustained elevations of AD-SoS values in all treated groups at day 19, while E2 caused a moderate increase that could be improved when combined with IOP (Sham: 1887.8 ± 14.87 m/s vs. Sham+IOP: 2026.0 ± 13.03 m/s; OVX: 1707.8 ± 18.82 m/s vs. OVX+IOP: 2009.0 ± 20.86 m/s; OVX+E2: 1779.6 ± 19.79 m/s vs. OVX+E2+IOP: 1986.4 ± 17.85 m/s) ($p < 0.05$). By the end of the study IOP brought about higher AD-SoS values (Sham: 1897.78 ± 38.65 m/s vs. Sham+IOP: 2019.15 ± 12.84 m/s; OVX: $1709.04 \pm$

24.14 m/s vs. OVX+IOP: 1950.6 ± 25.32 m/s; OVX+E2: 1900.27 ± 33.30 m/s vs. OVX+E2+IOP: 2023.7 ± 25.61 m/s) ($p < 0.05$).

4.3.2. Biomechanical changes

Ovariectomy caused a significant reduction of the $F_{\max}$ values of the tibias. As a result of IOP, increase of $F_{\max}$ (Sham: 160.11 ± 7.10 N vs. Sham+IOP: 218.60 ± 15.59 N; OVX: 69.61 ± 7.0 N vs. OVX+IOP: 150.25 ± 15.13 N; OVX+E2: 145.20 ± 10.53 N vs. OVX+E2+IOP: 190.80 ± 6.20 N) and a complete restoration of stiffness was observed in OVX rats (Sham: 766.2 ± 69.6 N/mm, Sham+IOP: 798.5 ± 19.5 N/mm; OVX: 563.1 ± 17.9 N/mm; OVX+IOP: 741.3 ± 50.6 N/mm; OVX+E2: 668.9 ± 47.3 N/mm; OVX+E2+IOP: 757.7 ± 66.7 N/mm) ($p < 0.05$).

4.3.3. Changes in calcium and phosphate content of the bone

At the end of the study, calcium mass concentration of the tibia was lower in the control OVX animals than in the SH ones. Calcium mass concentrations increased in IOP groups (Sham: 239.6 ± 1.8 mg/g, Sham+IOP: 257.3 ± 1.9 mg/g; OVX: 223.8 ± 3.9 mg/g; OVX+IOP: 234.4 ± 1.7 mg/g; OVX+E2: 233.9 ± 0.9 mg/g; OVX+E2+IOP: 242.9 ± 1.1 mg/g) ($p < 0.05$). Phosphate concentrations did not show significant changes in response to ovariectomy. IOP resulted in its considerable elevation in the sham-

operated and estrogen-treated OVX animals (Sham: 332.4 ± 0.4 mg/g vs. Sham+IOP: 334.4 ± 0.9 mg/g; OVX+E2: 332.3 ± 0.4 mg/g vs. OVX+E2+IOP: 336.2 ± 0.8 mg/g) ($p < 0.05$).

4.4. Undesirable effects

After iontophoresis erythema has been commonly occurred where the electrodes were placed before. This symptom usually resolved within a few hours. Other side-effect (e.g. burn) has not been observed.

5. Discussion

Several systemically administered efficient pharmacotherapies are available in the treatment of osteoporosis, however, local therapeutic modalities may also be useful to treat bone loss. Calcium ionostasis is used as an additional therapy of Complex Regional Pain Syndrome and delayed callus formation. Furthermore, results of some studies have suggested that iontophoresis of certain compounds may have beneficial effects on fracture healing or osteoporosis.

Our research group has previously developed a novel iontophoretic method protected by patent, that is based on the theoretical background of iontophoresis in general but differs from

the techniques ever used before. As a local treatment of osteoporosis, the utilization of the ‘three-electrode’ iontophoretic device and special calcium and phosphate donor microparticles may enable the simultaneous delivery of calcium and phosphate ions into the bone.

In this Ph.D. study, the effect of the novel calcium and phosphate iontophoresis was investigated through a series of *in vitro* and *in vivo* animal experiments. This is the first time in the literature when the targeted tissue of transdermal electrophoretic delivery is the bone. The aim of hormone and herbal medicine IOP trials was to deliver antiporotics into the blood or promoting local blood circulation. Magnesium and fluoride IOP was effective in enhancing bone mineralization in teeth, however it required a direct bone-electrode contact and the ion concentration was not measured. Due to the differences, the results of my Ph.D. work are not feasible to compare with data related to other IOPs in literature.

In vitro experiments were carried out on porcine tissue system in order to detect the effects of iontophoretic current and calcium and phosphate iontophoresis on the bone and soft tissues.

Without using calcium and phosphate donor molecules, iontophoretic current itself resulted in decreased calcium content of porcine muscle close to the anode side, although, it was still in the

physiological range. Current itself had no effect on skin or bone.

Applying ion donor molecules on the electrodes, IOP resulted in significantly increased calcium and phosphate content of the bone tissue. Thus, results of the *in vitro* experiments suggested that calcium and phosphate ions indeed penetrated into the bone by IOP.

However, other tissues located above the bone are not affected by the process, except skin contacting the electrodes. The enrichment of the compounds in the dermis is not surprising, as calcium- and phosphate-containing microparticles were applied on the electrodes, in close vicinity to the surface of the skin.

In conclusion, by means of this novel three-electrode iontophoretic apparatus and the use of calcium- and phosphate-donor microparticles, simultaneous calcium and phosphate targeted, transdermal delivery into bone is possible *in vitro*.

Results of the *in vivo* studies on ovariectomized versus sham-operated Sprague-Dawley rats indicated that simultaneous calcium and phosphate IOP treatment increased local bone density as shown by the increase in AD-SoS values both in the sham-operated and osteoporotic rats. Five times of IOP appeared to be steadily efficient as marked by a long lasting restoration of bone density values observed 72 days after the last treatment in all treated animal groups.

The same conclusion on effectiveness can be drawn from the results of the biomechanical tests. Data indicated that the novel IOP had a positive effect on the biomechanical parameters too as maximum load and stiffness values of the treated tibias increased. Elemental analysis provides further support for the findings described above. IOP increased the detected ion concentrations not only in ovariectomized rat tibias, but also in sham-operated animals.

The *in vivo* animal studies presented evidence for the efficacy of calcium and phosphate IOP concerning bone mineral contents, AD-SoS values and improved biomechanical properties of osteoporotic rat tibias without causing any harm on the experimental animals. Hence topical iontophoresis may represent an effective novel treatment modality in the management of bone loss.

The data of the comparative study showed that IOP and E2 monotherapy appeared to be similarly effective on reversing bone loss and the consequences induced by ovariectomy. Combination of the two modalities provided the highest efficacy on all parameters. Therefore combining IOP with other antiporotic approach may further improve the effectiveness.

The possible side-effects of calcium and phosphate iontophoresis

are the same as of other IOP treatment. Immediately after calcium and phosphate IOP, erythema has been occurred on the surface of the skin where the electrodes placed before. This symptom usually resolved within 3 hours without any intervention. Other side-effect (e.g. burn) has not been detected.

Limitation of this novel iontophoretic method emerges mainly from its topical applicability. Therefore, this technique may be restricted to areas where the electrodes can have a relatively close proximity to the targeted bone and to each other. Potential species-dependency of efficacy and limitations derived from the depth of penetration provided by the applied method would also restrict extrapolation of the results to humans. Treatment of the most affected areas of bone loss i.e. the vertebrae may require further technical modifications. The presented experimental model has also limitation as the relatively low number of animals and the limited clinical relevance of estrogen supplementation as a basis of comparison in osteoporotic women. For the above reasons, this novel approach may have therapeutic potential at local forms of bone loss such as algoneurodystrophy.

6. SUMMARY

In my Ph.D. study I aimed to perform *in vitro*, *in vivo* and *postmortem* animal experiments first in the world for the setting of a novel calcium and phosphate iontophoretic treatment, for the detection and clarification of its effects on bone.

The new results are summarized below:

- First in the literature both calcium and phosphate ions were simultaneously delivered transdermally into porcine bone by calcium and phosphate iontophoresis *in vitro*.
- It was proved, first time in literature, that calcium and phosphate iontophoresis has *in vivo* long-lasting effect on osteoporotic and normal rat tibias regarding AD-SoS values, biomechanical properties and mineral content improvement.
- A series of simultaneous calcium and phosphate iontophoresis compare to chronic estrogen therapy found to be similarly effective on the treatment of osteoporotic rat tibia, which effect can be enhanced by combining the two modalities.

These studies presented evidence for the efficacy of calcium and phosphate iontophoresis on osteoporotic bones. The results suggest that topical iontophoresis may be suitable for further *in vivo* utilization and probably for human use with limitations.

7. PUBLICATIONS

10.1. In extenso publications related to the dissertation

1. **Gomez, I.**, Szabó, A., Pap, L. Jr., Pap, L., Boda, K., Szekanecz, Z.: In vivo calcium and phosphate iontophoresis for the topical treatment of osteoporosis. *Phys Ther.* 92(2), 289-297, 2012. **IF: 3.113** (2011)
2. Pap, L.,*, **Gomez, I.**,*, Pap, L. Jr., Szabó, A., Szekanecz, Z.: Development of natural calcium- and phosphate-donating microparticles and a new iontophoretic apparatus for the topical treatment of local osteoporosis. Preliminary in vitro and in vivo studies. *Joint Bone Spine.* 77(5), 426-431, 2010. *Co-first authors with equal contribution. **IF: 2.46**

10.2. Other publications

3. Juhász, P., Mester, Á., Bíró, J., Héjj, G., Apáthy, Á., Bálint, P., Bazsó, A., Donáth, J., Gaál, R., **Gomez, I.**, Hittner, Gy., Hodinka, L., Hunka, A., Király, M., Kiss, Cs., Kiss, E., Korda, J., Márkus, I., Mikó, I., Orbán, I., Ormos, G., Ortutay, J., Penczner, G., Polgár, A., Ruzicska, É., Schmidt, Zs., Seszták, M., Sevcic, K., Sterba, G., Vereckei, E., Winkler, V., Poór, Gy.: A biológiai és a hagyományos betegségmódosító terápia hatékonyságának összehasonlító vizsgálata magyarországi

- rheumatoid arthritises betegekben: az ABRAB-vizsgálat első eredményei. Magyar Reumatol. 53(2), 63-73, 2012.
4. **Gomez,I.**, Nagy,D., Seszták,M., Vereckei,E., Csauth,K., Farkas, P., Hodinka,L.: Szeptikus arthritisek diagnosztikai kihívásai két eset kapcsán. Magyar Reumatol. 52(4), 207-212, 2011.
 5. Gomez R, **Gomez I**: Reumatológiai szakrendelésen javasolt fizioterápiás kezelések: szokás, hagyomány vagy hatékonyság? Balneológia, Gyógyfürdőügy, Gyógyidegenforgalom. 30(1), 19-26, 2011.
 6. Szabó, A., Hartmann, P., Varga, R., Jánvári, K., Lendvai, Z., Szalai, I., **Gomez, I.**, Varga, G., Greksa, F., Németh, I., Rázga, Z., Keresztes, M., Garab, D., Boros, M.: Periosteal microcirculatory action of chronic estrogen supplementation in osteoporotic rats challenged with tourniquet ischemia. Life Sci. 88(3-4), 156-162, 2011. **IF:2,597**
 7. Pap, L., Buday, T., Papp, I., **Gomez, I.**: Brief notes on previous and recent results of thermoanalytical research of bone. Acta geogr. Geol. Meteorol. Debr. 3, 15-22, 2008.
 8. Gomez, R., **Gomez, I.**: A termálvíz gyógyhatásának vizsgálata térdarthrózisban. Balneológia, Gyógyfürdőügy, Gyógyidegenforgalom. 24(1), 39-48, 2005.
 9. Gomez, R., Szunyogi, T., **Gomez, I.**: Pszichoterápia a debreceni

gyógyfürdőben. Balneológia, Gyógyfürdőügy,
Gyógyidegenforgalom. 23(2), 40-48, 2004.

10. Gomez, R., **Gomez, I.**: A debreceni termálvíz hatásosságának vizsgálata térdarthrózisban. Debreceni Szle. 12(1), 25-31, 2004.

Total IF: 8.1

Total IF (publications related to the dissertation): 5.573

10.3. Abstracts

11. **Gomez, I.**, Pap, L., Szabó, A., Boda, K., Szekanecz, Z.: In vivo calcium and phosphate iontophoresis on osteoporotic rat tibia. A new method for the topical treatment of osteoporosis. Eur. J. Clin. Invest. 42 (Suppl.1), 66-67, 2012.
12. **Gomez, I.**, Nagy, D., Csákvári, D., Donáth, J., Seszták, M., Vereckei, E., Csauth, K., Farkas, P., Hodinka, L.: Diagnostic challenges of septic arthritis in the daily clinical practice. Three case reports. Reumatologia. 50(4), Suppl.1, S44, 2012.
13. **Gomez, I.**, Mikó, I., Hodinka, L.: Tumoros betegek fizioterápiás ellátásának korszerű elvei. Magy. Reumatol. 53(3), 167-168, 2012.
14. **Gomez, I.**: Katepszin-K inhibitorok: Új terápiás célpont az osteoporosis kezelésében. Magy. Reumatol. 53, 38, 2012.
15. **Gomez, I.**, Nagy, D., Seszták, M., Vereckei, E., Csauth, K.,

- Farkas, P., Hodinka, L.: Infektív arthritisek diagnosztikai kihívásai két eset kapcsán. *Magy. Reumatol.* 52(3), 146, 2011.
16. **Gomez, I.:** Elektroterápia csontrendszeri vonatkozásai EBM-adatok tükrében. *Magyar Reumatol.* 52(2), 115, 2011.
17. **Gomez, I., Szabó, A., Papp, L., Szekanecz, Z.:** In vivo calcium and phosphate iontophoresis for the topical treatment of osteoporosis. *Ann. Rheum. Dis.* 70 (Suppl.3.), 360, 2011.
18. Pap, L., **Gomez, I.,** Pap, L. Jr., Szabó, A., Szekanecz, Z.: Development of natural calcium- and phosphate-donating molecules and a new iontophoretic device for the topical treatment of osteoporosis. Preliminary in vitro and in vivo studies. *Arthritis and Rheumatism*, Philadelphia, 223, 2009.
19. **Gomez, I.,** Pap, L., Szabó, A., Boros, M., Szekanecz, Z.: Calcium and phosphate delivery into osteoporotic rat tibia by a new iontophoretic treatment in vivo. *Ann. Rheum. Dis.* 67 (Suppl.1.), A50-A51, 2008.
20. **Gomez, I.:** Osteoporoticus patkánycsontokon iontoforetikus kezeléssel elért eredmények. *Magy. Reumatol.* 48, 116, 2007.
21. Varga, R., Szabó, A., **Gomez, I.,** Jánvári, K., Varga, G., Pap, L., Boros, M.: Responses of the tibial microcirculation to local iontophoretic treatment of osteopenia in rats. *Eur. Surg. Res.* 38 (Suppl.1), 51-52, 2006.

10.4. Referatum

22. **Gomez I:** Gyógyszeres terápia a csonttörés kockázatának csökkentésére: Észrevételek az ACR clinical practice guideline-jaival kapcsolatban. Immunol. Szle. 1(3-4), 42, 2009.

(Ismeretett mű: Lewicki E.M: Pharmacologic therapy to reduce fracture risk: comment on the clinical practice guidelines of the ACP. In: Nature Reviews Rheumatology. – 5 : 3 p. 120-121)

Register Number: DEENKÉTK/97/2013.

Item Number:

Subject: Ph.D. List of Publications

Candidate: Izabella Gomez

Neptun ID: ZKG15A

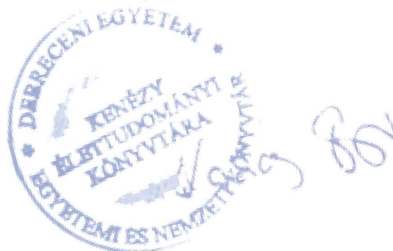
Doctoral School: Doctoral School of Clinical Medicine

List of publications related to the dissertation

1. **Gomez, I.**, Szabó, A., jr. Pap, L., Pap, L., Boda, K., Szekanecz, Z.: In Vivo Calcium and Phosphate Iontophoresis for the Topical Treatment of Osteoporosis.
Phys. Ther. 92 (2), 289-297, 2012.
DOI: <http://dx.doi.org/10.2522/ptj.20100400>
IF:3.113 (2011)

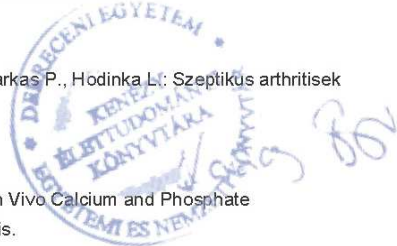
- *2. Pap, L., **Gomez, I.**, jr. Pap, L., Szabó, A., Szekanecz, Z.: Development of natural calcium- and phosphate-donating microparticles and a new iontophoretic apparatus for the topical treatment of local osteoporosis. Preliminary in vitro and in vivo studies.
Joint Bone Spine. 77 (5), 426-431, 2010.
DOI: <http://dx.doi.org/10.1016/j.jbspin.2010.02.039>
IF:2.46

*Co-first authors with equal contribution.



List of other publications

3. **Gomez, I.,** Pap, L., Szabó, A., Boda, K., Szekanecz, Z.: In vivo calcium and phosphate iontophoresis on osteoporotic rat tibia. A new method for the topical treatment of osteoporosis.
Eur. J. Clin. Invest. 42 (Suppl.1), 66-67, 2012.
DOI: <http://dx.doi.org/10.1111/j.1365-2362.2012.02650.x>
4. **Gomez, I.,** Nagy, D., Csákvári, D., Donáth, J., Seszták, M., Vereckei, E., Csauth, K., Farkas, P., Hodinka, L.: Diagnostic challenges of septic arthritis in the daily clinical practice. Three case reports.
Reumatologia. 50,4 (Suppl.1), Suppl.1 (2012), p. S44, 2012.
5. **Gomez I.I.,** Mikó I., Hodinka L.: Tumoros betegek fizioterápiás ellátásának korszerű elvei.
Magyar Reumatol. 53 (3), 167-168, 2012.
6. **Gomez I.:** Katepszin-K inhibitorok: Új terápiás célpont az osteoporosis kezelésében.
Magyar Reumatol. 53, 38, 2012.
7. Juhász P., Mester Á., Bíró J., Héjji G., Apáthy Á., Bálint P., Bazsó A., Donáth J., Gaál R., **Gomez I.,** Hittner G., Hodinka L., Hunka A., Király M., Kiss C., Kiss E., Korda J., Márkus I., Mikó I., Orbán I., Ormos G., Ortutay J., Penczner G., Polgár A., Ruzicska É., Schmidt Z., Seszták M., Sevcic K., Sterba G., Vereckei E., Winkler V., Poór G.: A biológiai és a hagyományos betegségmódosító terápia hatékonyságának összehasonlító vizsgálata magyarországi reumatoid arthritises betegekben: Az ABRAB-vizsgálat első eredményei.
Magyar Reumatol. 53 (2), 63-73, 2012.
8. **Gomez I.,** Nagy D., Csákvári D., Donáth J., Seszták M., Vereckei E., Csauth K., Farkas P., Hodinka L.: Infektív arthritisek diagnosztikai kihívásai két eset kapcsán.
Magyar Reumatol. 52 (3), 146, 2011.
9. **Gomez I.:** Elektroterápia csontrendszeri vonatkozásai EBM-adatok tükrében.
Magyar Reumatol. 52 (2), 115, 2011.
10. **Gomez I.,** Nagy D., Seszták M., Vereckei E., Csauth K., Farkas P., Hodinka L.: Szeptikus arthritisek diagnosztikai kihívásai két eset kapcsán.
Magyar Reumatol. 52, 207-212, 2011.
11. **Gomez, I.,** Szabó, A., Papp, L., Papp, L., Szekanecz, Z.: In Vivo Calcium and Phosphate Iontophoresis for the Topical Treatment of Osteoporosis.
Ann. Rheum. Dis. 70 (Suppl.3), 360, 2011.



12. Gómez R., **Gomez I.**: Reumatológiai szakrendelésen javasolt fizioterápiás kezelések: Szokás, hagyomány vagy hatékonyság?
Balneológia, gyógyfürdőügy, gyógyidegenforgalom. 30 (1), 19-26, 2011.
13. Szabó, A., Hartmann, P., Varga, R., Jánvári, K., Lendvai, Z., Szalai, I., **Gomez, I.**, Varga, G., Greksa, F., Németh, I., Rázga, Z., Keresztes, M., Garab, D., Boros, M.: Periosteal microcirculatory action of chronic estrogen supplementation in osteoporotic rats challenged with tourniquet ischemia.
Life Sci. 88 (3-4), 156-162, 2011.
DOI: <http://dx.doi.org/10.1016/j.lfs.2010.11.004>
IF:2.527
14. **Gomez I.**: Gyógyszeres terápia a csonttörés kockázatának csökkentésére: Észrevételek az ACP clinical practice guideline-jaival kapcsolatban.
Immunol. Szle. 1 (3-4), 42, 2009.
(Ismertetett mű : Lewiecki E. M : Pharmacologic therapy to reduce fracture risk: comment on the clinical practice guidelines of the ACP. In: Nature Reviews Rheumatology. - 5 : 3 p. 120-121)
15. Pap, L., **Gomez, I.**, jr. Pap, L., Szabó, A., Szekanecz, Z.: Development of natural calcium- and phosphate-donating molecules and a new iontophoretic device for the topical treatment of osteoporosis. Preliminary in vitro and in vivo studies.
In: Arthritis and Rheumatism. Arthritis and Rheumatism, [Philadelphia], 223, 2009.
16. **Gomez, I.**, Pap, L., Szabó, A., Boros, M., Szekanecz, Z.: Calcium and phosphate delivery into osteoporotic rat tibia by a new iontophoretic treatment in vivo.
Ann. Rheum. Dis. 67 (Suppl.1.), A50-A51, 2008.
17. Pap, L., Buday, T., Papp, I., **Gomez, I.**: Brief notes on previous and recent results of thermoanalytical research of bone.
Acta geogr. geol. meteorol. Debr. 3, 15-22, 2008.
18. **Gomez I.**: Osteoporotikus patkánycsontokon iontoforetikus kezeléssel elért eredmények.
Magyar Reumatol. 48, 116, 2007.
19. Varga, R., Szabó, A., **Gomez, I.**, Jánvári, K., Varga, G., Pap, L., Boros, M.: Responses Of The Tibial Microcirculation To Local Iontophoretic Treatment For Osteopenia In Rats.
Eur. Surg. Res. 38 (Suppl.1), 51-52, 2006.
20. Gómez R., **Gomez I.**: A termálvíz gyógyhatásának vizsgálata térdarthrózisban.
Balneológia, gyógyfürdőügy, gyógyidegenforgalom. 24. (1.), 39-48, 2005.

21. Gómez R., Szunyogi T., **Gomez I.**: Pszichoterápia a debreceni gyógyfürdőben.

Balneológia, gyógyfürdőügy, gyógyidegenforgalom. 23 (2), 40-48, 2004.

22. Gómez R., **Gomez I.**: A debreceni termálvíz hatásosságának vizsgálata térdarthrózisban.

Debreceni Szle. 1, 25-31, 2004.

Total IF: 8.1

Total IF (publications related to the dissertation): 5.573

The Candidate's publication data submitted to the Publication Database of the University of Debrecen have been validated by Kenezy Life Sciences Library on the basis of Web of Science, Scopus and Journal Citation Report (Impact Factor) databases.

05 March, 2013

