·基础研究·

# 中医“肝肾同源”理论异病同治膝骨关节炎和绝经后骨质疏松症的实验理论基础研究

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**摘　要　目的:**从骨代谢角度探讨依据中医“肝肾同源”理论异病同治膝骨关节炎(knee osteoarthritis,KOA)和绝经后骨质疏松症(postmenopausal osteoporosis,PMOP)的实验理论基础。**方法:**将 60 只 8 月龄 SPF 级雌性 SD 大鼠随机分为空白组、KOA 组和 PMOP 组。空白组大鼠不进行任何处理,KOA 组和 PMOP 组分别采用改良 Hulth 法和去卵巢法制作 KOA 和 PMOP 大鼠模型。分别于造模后 7、28、56 d 从各组随机选取 6 只大鼠测定股骨骨密度,抽取腹主动脉血测定血清中抗酒石酸酸性磷酸酶 5b(tartrate resistant acid phosphatase－5b,TRACP－5b)、骨碱性磷酸酶(bone alkaline phosphatase,BALP)、Ⅰ型前胶原氨基端前肽(N－terminal propeptide of type Ⅰ precollagen,PⅠNP)、Ⅰ型前胶原羧基端前肽(C－terminal propeptide of type Ⅰ precollagen,PⅠCP)、Ⅰ型胶原羧基端交联端肽(C－terminal cross－linked telopeptides of type Ⅰ collagen,CTX－Ⅰ)、Ⅰ型胶原氨基端交联端肽(N－terminal cross－linked telopeptides of type Ⅰ collagen,NTX－Ⅰ)、白细胞介素－1β(interleukin－1β,IL－1β)、IL－6、IL－8、IL－10、肿瘤坏死因子－α(tumor necrosis factor－α,TNF－α)、基质金属蛋白酶－9(matrix metalloproteinase－9,MMP－9)及 MMP－13 含量,切取双侧后肢膝关节软骨组织制成切片,在光镜下观察其形态,并采用 Mankin’s 评分标准进行评分。**结果:**造模后 7、28、56 d 时各组大鼠股骨骨密度和血清中 TRACP－5b、BALP、PⅠNP、PⅠCP、CTX－Ⅰ、NTX－Ⅰ、IL－1β、IL－6、IL－8、IL－10、TNF－α、MMP－9、MMP－13 含量及膝关节软骨 Mankin’s 评分总体比较,组间差异均有统计学意义。造模后 7 d 时,KOA 组与空白组骨密度比较,差异无统计学意义($P=0.059$),PMOP 组骨密度低于空白组($P=0.005$);造模后 28、56 d 时,KOA 组和 PMOP 组骨密度均低于空白组($P=0.000$,$P=0.002$;$P=0.003$,$P=0.000$)。造模后各时点 KOA 组和 PMOP 组血清 TRACP－5b 浓度均高于空白组($P=0.015$,$P=0.013$,$P=0.000$;$P=0.000$,$P=0.000$,$P=0.000$),BALP 浓度均高于空白组($P=0.000$,$P=0.003$,$P=0.001$;$P=0.000$,$P=0.000$,$P=0.000$),PⅠNP 浓度均低于空白组($P=0.000$,$P=0.003$,$P=0.000$;$P=0.000$,$P=0.000$,$P=0.000$),PⅠCP 浓度均低于空白组($P=0.005$,$P=0.000$,$P=0.001$;$P=0.000$,$P=0.005$,$P=0.000$),CTX－Ⅰ浓度均高于空白组($P=0.000$,$P=0.002$,$P=0.003$;$P=0.000$,$P=0.000$,$P=0.000$),NTX－Ⅰ浓度均高于空白组($P=0.000$,$P=0.000$,$P=0.008$;$P=0.005$,$P=0.003$,$P=0.000$),IL－1β 浓度均高于空白组($P=0.023$,$P=0.003$,$P=0.006$;$P=0.013$,$P=0.006$,$P=0.003$),IL－8 浓度均高于空白组($P=0.000$,$P=0.000$,$P=0.000$;$P=0.008$,$P=0.000$,$P=0.000$),IL－10 浓度均低于空白组($P=0.032$,$P=0.029$,$P=0.013$;$P=0.010$,$P=0.000$,$P=0.000$),TNF－α 浓度均高于空白组($P=0.000$,$P=0.000$,$P=0.009$;$P=0.000$,$P=0.016$,$P=0.006$);造模后各时点 KOA 组血清 IL－6 浓度均高于空白组($P=0.026$,$P=0.003$,$P=0.000$),造模后 28、56 d 时 PMOP 组血清 IL－6 浓度均高于空白组($P=0.023$,$P=0.006$),造模后 7 d 时 PMOP 组血清 IL－6 浓度与空白组比较,差异无统计学意义($P=0.068$)。造模后各时点 KOA 组和 PMOP 组血清 MMP－9 浓度均高于空白组($P=0.000$,$P=0.021$,$P=0.002$;$P=0.002$,$P=0.018$,$P=0.000$),MMP－13 浓度均高于空白组($P=0.000$,$P=0.000$,$P=0.000$;$P=0.000$,$P=0.010$,$P=0.000$)。造模后各时点 KOA 组关节软骨 Mankin’s 评分均高于空白组($P=0.000$,$P=0.000$,$P=0.000$);造模后 7、28 d 时,PMOP 组 Mankin’s 评分与空白组比较,差异均无统计学意义($P=0.082$,$P=0.056$),造模后 56 d 时 PMOP 组 Mankin’s 评分高于空白组($P=0.043$)。**结论:**KOA 从早期开始即存在与 PMOP 类似的高转换型骨代谢紊乱,而 PMOP 中后期也会出现类似 KOA 的软骨退变;高转换型骨代谢紊乱可能在 KOA 和 PMOP 的发病中具有同样重要的作用,这可作为中医学根据“肝肾同源”理论对 KOA 和 PMOP 进行异病同治的实验理论基础。

**关键词　骨关节炎,膝;骨质疏松,绝经后;肝肾同源;异病同治;动物实验;大鼠,**Sprague－Dawley

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## Application of TCM theory of HOMOGENY OF LIVER AND KIDNEY and TREATING DIFFERENT DISEASES WITH SAME METHOD to treatment of knee osteoarthritis and postmenopausal osteoporosis: an experimental research of theoretical foundation

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**ABSTRACT** **Objective**: To explore the experimental theoretical foundation for treating knee osteoarthritis (KOA) and postmenopausal osteoporosis (PMOP) with same method under the guidance of TCM theory of HOMOGENY OF LIVER AND KIDNEY through bone metabolism experimentation. **Methods**: Sixty 8-month-old SPF-grade female SD rats were randomly divided into blank group, KOA group and PMOP group. The rats in blank group did not receive any treatment, while the KOA rat models were built by using improved Hulth method in KOA group and the PMOP rat models were built by ovariectomy in PMOP group. Six rats were randomly selected from each group at 7, 28 and 56 days after the modeling respectively and their femoral bone mineral densities (BMD) were measured. Their blood was drawn from abdominal aorta and the serum contents of tartrate resistant acid phosphatase-5b (TRACP-5b), bone alkaline phosphatase (BALP), N-terminal propeptide of type Ⅰ precollagen (PⅠNP), C-terminal propeptide of type Ⅰ precollagen (PⅠCP), C-terminal cross-linked telopeptides of type Ⅰ collagen (CTX-Ⅰ), N-terminal cross-linked telopeptides of type Ⅰ collagen (NTX-Ⅰ), interleukin-1β (IL-1β), IL-6, IL-8, IL-10, tumor necrosis factor-α (TNF-α), matrix metalloproteinase-9 (MMP-9) and MMP-13 were measured. The knee articular cartilage tissues of bilateral posterior limbs were sectioned for HE staining and their morphous were observed under light microscope and were evaluated by using Mankin's scoring standard. **Results**: There was statistical difference in femoral BMD and serum contents of TRACP-5b, BALP, PⅠNP, PⅠCP, CTX-Ⅰ, NTX-Ⅰ, IL-1β, IL-6, IL-8, IL-10, TNF-α, MMP-9, MMP-13 and Mankin's scores of knee articular cartilage between the 3 groups at 7, 28 and 56 days after the modeling respectively. There was no statistical difference in femoral BMD between KOA group and blank group ($P=0.059$) and the femoral BMD were lower in PMOP group compared to blank group ($P=0.005$) at 7 day after the modeling. The femoral BMD were lower in KOA group and PMOP group compared to blank group at 28 and 56 days after the modeling ($P=0.000$, $P=0.002$; $P=0.003$, $P=0.000$). At each time point after the modeling, the serum concentration of TRACP-5b were higher in KOA group and PMOP group compared to blank group ($P=0.015$, $P=0.013$, $P=0.000$; $P=0.000$, $P=0.000$, $P=0.000$), the serum concentration of BALP were higher in KOA group and PMOP group compared to blank group ($P=0.000$, $P=0.003$, $P=0.001$; $P=0.000$, $P=0.000$, $P=0.000$), the serum concentration of PⅠNP were lower in KOA group and PMOP group compared to blank group ($P=0.000$, $P=0.003$, $P=0.000$; $P=0.000$, $P=0.000$, $P=0.000$), the serum concentration of PⅠCP were lower in KOA group and PMOP group compared to blank group ($P=0.005$, $P=0.000$, $P=0.001$; $P=0.000$, $P=0.005$, $P=0.000$), the serum concentration of CTX-Ⅰ were higher in KOA group and PMOP group compared to blank group ($P=0.000$, $P=0.002$, $P=0.003$; $P=0.000$, $P=0.000$, $P=0.000$), the serum concentration of NTX-Ⅰ were higher in KOA group and PMOP group compared to blank group ($P=0.000$, $P=0.000$, $P=0.008$; $P=0.005$, $P=0.003$, $P=0.000$), the serum concentration of IL-1β were higher in KOA group and PMOP group compared to blank group ($P=0.023$, $P=0.003$, $P=0.006$; $P=0.013$, $P=0.006$, $P=0.003$), the serum concentration of IL-8 were higher in KOA group and PMOP group compared to blank group ($P=0.000$, $P=0.000$, $P=0.000$; $P=0.008$, $P=0.000$, $P=0.000$), the serum concentration of IL-10 were lower in KOA group and PMOP group compared to blank group ($P=0.032$, $P=0.029$, $P=0.013$; $P=0.010$, $P=0.000$, $P=0.000$), the serum concentration of TNF-α were higher in KOA group and PMOP group compared to blank group ($P=0.000$, $P=0.000$, $P=0.009$; $P=0.000$, $P=0.016$, $P=0.006$). The serum concentration of IL-6 were higher in KOA group compared to blank group at each time point after the modeling ($P=0.026$, $P=0.003$, $P=0.000$). The serum concentration of IL-6 were higher in PMOP group compared to blank group at 28 and 56 days after the modeling ($P=0.023$, $P=0.006$). There was no statistical difference in serum concentration of IL-6 between PMOP group and blank group at 7 day after the modeling ($P=0.068$). At each time point after the modeling, the serum concentration of MMP-9 were higher in KOA group and PMOP group compared to blank group ($P=0.000$, $P=0.021$, $P=0.002$; $P=0.002$, $P=0.018$, $P=0.000$), the serum concentration of MMP-13 were higher in KOA group and PMOP group compared to blank group ($P=0.000$, $P=0.000$, $P=0.000$; $P=0.000$, $P=0.010$, $P=0.000$). The Mankin's scores of knee articular cartilage were higher in KOA group compared to blank group at each time point after the modeling ($P=0.000$, $P=0.000$, $P=0.000$). There was no statistical difference in Mankin's scores of knee articular cartilage between PMOP group and blank group at 7 and 28 days after the modeling ($P=0.082$, $P=0.056$). The Mankin's scores of knee articular cartilage were higher in PMOP group compared to blank group at 56 days after the modeling ($P=0.043$). **Conclusion**: The high-turnover-type bone metabolic

disorder can be found in KOA from the early period and the cartilage degeneration can be found in PMOP in the middle and later period,so PMOP is similar to KOA in these features. The high – turnover – type bone metabolic disorder may play an equally important role in morbidity of KOA and PMOP,so it can be considered as the experimental theoretical foundation for treating KOA and PMOP with same method according to the TCM theory of HOMOGENY OF LIVER AND KIDNEY.

**Key words** osteoarthritis,knee;osteoporosis,postmenopausal;homogeny of liver and kidney;treating different diseases with same method;animal experimentation;rats,Sprague – Dawley

膝骨关节炎(knee osteoarthritis,KOA)主要以关节软骨退行性改变,骨、软骨以及其他结缔组织增生为特征[1];骨质疏松症(osteoporosis,OP)则主要表现为全身骨量减少、骨的显微结构破坏,导致骨脆性增加、容易发生骨折。KOA 患者的骨密度通常不下降,部分患者的骨密度还会增高[2],而 OP 的典型表现则是骨密度降低。但二者的流行病学特点非常相似,如均多见于中老年人、女性多于男性,且均以绝经后女性多见[3]。因此对于二者是否存在共同的发病机制一直存在较多的争议[4-7],其潜在的机制一直是研究的热点[8-13]。通过回顾文献我们发现,这些争议与部分研究中未能明确所纳入 KOA、OP 患者的病理类型有关,在这两类疾病中绝经后 OP(postmenopausal osteoporosis,PMOP)与早期 KOA 的联系最为紧密。

KOA 和 PMOP 在中医学中可分别归属于“膝痹”“骨痹”和“骨痿”“痿证”范畴。“膝痹”病位在膝,膝为筋府,为肝所主;“骨痿”病位在“骨”,为肾脏所主。中医理论认为肝肾两脏关系密切,有“肝肾同源”之说,在采用补益肝肾、滋阴养血法对这 2 种疾病进行异病同治方面也进行了大量的临床实践,理、法、方、药均非常成熟,但相关的基础研究较少。我们结合文献和部分前期实验结果,将骨代谢作为研究的切入点,设计了动物实验,探讨依据中医“肝肾同源”理论异病同治 KOA 和 PMOP 的实验理论基础,现总结报告如下。

## 1 材料与仪器

**1.1 实验动物** 8 月龄 SPF 级雌性 SD 大鼠 60 只,体质量 440 ~ 470 g,购自北京维通利华实验动物技术有限公司,实验动物许可证号:SCXK(京)20160001。实验方案经实验动物医学伦理委员会审核通过。

**1.2 试剂和仪器** 戊巴比妥钠(Sigma),丁胺卡那霉素(10 万单位,江苏正天药业有限公司),伊红染色液、苏木素染色液(上海太阳生物技术有限公司),大鼠抗酒石酸酸性磷酸酶 5b(tartrate resistant acid phosphatase – 5b,TRACP – 5b)、骨碱性磷酸酶(bone alkaline phosphatase,BALP)、Ⅰ型前胶原氨基端前肽(N – terminal propeptide of type Ⅰ precollagen,P Ⅰ NP)、Ⅰ型前胶原羧基端前肽(C – terminal propeptide of type Ⅰ precollagen,P Ⅰ CP)、Ⅰ型胶原羧基端交联端肽(C – terminal cross – linked telopeptides of type Ⅰ collagen,CTX – Ⅰ)、Ⅰ型胶原氨基端交联端肽(N – terminal cross – linked telopeptides of type Ⅰ collagen,NTX – Ⅰ)、白细胞介素 – 1β(interleukin – 1β,IL – 1β)、IL – 6、IL – 8、IL – 10、肿瘤坏死因子 – α(tumor necrosis factor – α,TNF – α)、基质金属蛋白酶 – 9(matrix metalloproteinase – 9,MMP – 9)及 MMP – 13 ELISA 试剂盒(上海朗顿生物技术有限公司);MEDIX – 90双能 X 线骨密度仪(Medlink),CKX – 31 光学显微镜(Olympus)。

## 2 方 法

**2.1 分组及造模** 适应性喂养 1 周后,将 60 只大鼠随机分为空白组、KOA 组和 PMOP 组,每组 20 只。空白组大鼠不进行任何处理,KOA 组和 PMOP 组大鼠分别采用改良 Hulth 法和去卵巢法制作 KOA 和 PMOP 模型,具体方法如下:KOA 组大鼠禁食 12 h 后腹腔注射 3% 戊巴比妥钠(30 mg · $kg^{-1}$),麻醉起效后经膝前正中切口直视下切断双侧后肢前交叉韧带,逐层缝合;PMOP 组大鼠禁食 12 h 后腹腔注射 3% 戊巴比妥钠(30 mg · $kg^{-1}$),麻醉起效后在背部两侧腰椎旁 1 ~ 1.5 cm 处纵形切开入腹,结扎双侧卵巢动脉,切除双侧卵巢,逐层缝合。术后 KOA 组和 PMOP 组大鼠按 10 mg · $kg^{-1}$肌肉注射丁胺卡那霉素,连续 4 d,每天 1 次。各组大鼠均分笼饲养,自由饮水和进食,动物房采用自然光暗周期,室温(25 ± 2)℃,相对湿度(60 ± 5)%。

**2.2 实验指标测定** 分别于造模后 7、28、56 d 从各组随机选取 6 只大鼠进行股骨骨密度、血清中骨代谢标记物和 OA 相关指标、软骨组织病理学检查。

骨密度检查采用双能 X 线骨密度仪测量大鼠双侧股骨骨密度,取平均值。骨密度测定完成后将所选

大鼠空腹 12 h,从腹主动脉取血 10 mL,注入预冷的装有 1% 肝素的塑料试管内,混匀后在 4 ℃以 2500 r·min$^{-1}$离心 12 min(离心半径 10 cm),取上清液置于 -20 ℃冰箱中备用。按照 ELISA 试剂盒说明测定大鼠血清中 TRACP-5b、BALP、PⅠNP、PⅠCP、CTX-Ⅰ、NTX-Ⅰ、IL-1β、IL-6、IL-8、IL-10、TNF-α、MMP-9、MMP-13 的含量。腹主动脉取血后以 $CO_2$ 窒息法处死大鼠,在双侧后肢胫骨平台上下 3~5 mm 处截取软骨组织,经常规固定、包埋、切片、HE 染色,光镜下观察其形态,并采用 Mankin's 评分标准[8]进行评分。

**2.3　数据统计分析**　采用 SPSS 11.0 软件进行数据统计分析,3 组大鼠造模后不同时点的股骨骨密度、软骨 Mankin's 评分及血清中 TRACP-5b、BALP、PⅠNP、PⅠCP、CTX-Ⅰ、NTX-Ⅰ、IL-1β、IL-6、IL-8、IL-10、TNF-α、MMP-9、MMP-13 含量的总体比较均采用单因素方差分析,组间两两比较采用 LSD-$t$ 检验。检验水准 $\alpha=0.05$。

## 3　结　果

造模后 7、28、56 d 时各组大鼠股骨骨密度比较,差异均有统计学意义。造模后 7 d 时,KOA 组与空白组骨密度比较,差异无统计学意义($P=0.059$);PMOP 组骨密度低于空白组($P=0.005$)。造模后 28、56 d 时,KOA 组和 PMOP 组骨密度均低于空白组($P=0.000$,$P=0.002$;$P=0.003$,$P=0.000$)。见表 1。

造模后 7、28、56 d 时各组大鼠血清 TRACP-5b 浓度比较,差异均有统计学意义。造模后各时点 KOA 组和 PMOP 组血清 TRACP-5b 浓度均高于空白组($P=0.015$,$P=0.013$,$P=0.000$;$P=0.000$,$P=0.000$,$P=0.000$)。见表 2。

造模后 7、28、56 d 时各组大鼠血清 BALP 浓度比较,差异均有统计学意义。造模后各时点 KOA 组和 PMOP 组血清 BALP 浓度均高于空白组($P=0.000$,$P=0.003$,$P=0.001$;$P=0.000$,$P=0.000$,$P=0.000$)。见表 3。

造模后 7、28、56 d 时各组大鼠血清 PⅠNP 浓度比较,差异均有统计学意义。造模后各时点 KOA 组和 PMOP 组血清 PⅠNP 浓度均低于空白组($P=0.000$,$P=0.003$,$P=0.000$;$P=0.000$,$P=0.000$,$P=0.000$)。见表 4。

**表 1　3 组大鼠造模后不同时点股骨骨密度比较**　$\bar{x}\pm s$,g·cm$^{-2}$

| 组别 | 样本量(只) | 造模后 7 d | 造模后 28 d | 造模后 56 d |
|---|---|---|---|---|
| 空白组 | 6 | 0.464±0.014 | 0.460±0.020 | 0.462±0.023 |
| KOA 组 | 6 | 0.407±0.064 | 0.382±0.010 | 0.352±0.029 |
| PMOP 组 | 6 | 0.326±0.016 | 0.225±0.008 | 0.140±0.029 |
| $F$ 值 | | 9.451 | 236.441 | 110.412 |
| $P$ 值 | | 0.014 | 0.000 | 0.000 |

**表 2　3 组大鼠造模后不同时点血清 TRACP-5b 浓度比较**　$\bar{x}\pm s$,μmol·L$^{-1}$

| 组别 | 样本量(只) | 造模后 7 d | 造模后 28 d | 造模后 56 d |
|---|---|---|---|---|
| 空白组 | 6 | 3.208±0.090 | 3.452±0.110 | 3.560±0.023 |
| KOA 组 | 6 | 6.277±0.075 | 6.252±0.040 | 5.048±0.046 |
| PMOP 组 | 6 | 6.235±0.041 | 6.235±0.041 | 6.208±0.090 |
| $F$ 值 | | 1 804.577 | 1 514.139 | 1 466.404 |
| $P$ 值 | | 0.000 | 0.000 | 0.000 |

**表 3　3 组大鼠造模后不同时点血清 BALP 浓度比较**　$\bar{x}\pm s$,ng·mL$^{-1}$

| 组别 | 样本量(只) | 造模后 7 d | 造模后 28 d | 造模后 56 d |
|---|---|---|---|---|
| 空白组 | 6 | 2.558±0.031 | 2.613±0.063 | 2.584±0.050 |
| KOA 组 | 6 | 2.975±0.033 | 3.540±0.092 | 2.875±0.020 |
| PMOP 组 | 6 | 2.695±0.064 | 3.104±0.081 | 3.177±0.023 |
| $F$ 值 | | 66.745 | 102.518 | 234.808 |
| $P$ 值 | | 0.000 | 0.000 | 0.000 |

表 4 3 组大鼠造模后不同时点血清 PⅠNP 浓度比较 $\bar{x} \pm s$,ng · mL$^{-1}$

| 组别 | 样本量(只) | 造模后 7 d | 造模后 28 d | 造模后 56 d |
|---|---|---|---|---|
| 空白组 | 6 | 183.917 ± 2.391 | 183.800 ± 5.565 | 181.300 ± 2.403 |
| KOA 组 | 6 | 146.967 ± 4.053 | 116.600 ± 0.600 | 113.817 ± 1.487 |
| PMOP 组 | 6 | 157.367 ± 2.063 | 109.067 ± 2.415 | 107.583 ± 0.840 |
| *F* 值 | | 123.794 | 410.042 | 3 079.441 |
| *P* 值 | | 0.000 | 0.000 | 0.000 |

造模后 7、28、56 d 时各组大鼠血清 PⅠCP 浓度比较,差异均有统计学意义。造模后各时点 KOA 组和 PMOP 组血清 PⅠCP 浓度均低于空白组（$P = 0.005$, $P = 0.000$, $P = 0.001$; $P = 0.000$, $P = 0.005$, $P = 0.000$）。见表 5。

造模后 7、28、56 d 时各组大鼠血清 CTX－Ⅰ浓度比较,差异均有统计学意义。造模后各时点 KOA 组和 PMOP 组血清 CTX－Ⅰ浓度均高于空白组（$P = 0.000$, $P = 0.002$, $P = 0.003$; $P = 0.000$, $P = 0.000$, $P = 0.000$）。见表 6。

造模后 7、28、56 d 时各组大鼠血清 NTX－Ⅰ浓度比较,差异均有统计学意义。造模后各时点 KOA 组和 PMOP 组血清 NTX－Ⅰ浓度均高于空白组（$P = 0.000$, $P = 0.000$, $P = 0.008$; $P = 0.005$, $P = 0.003$, $P = 0.000$）。见表 7。

造模后 7、28、56 d 时各组大鼠血清 IL－1β 浓度比较,差异均有统计学意义。造模后各时点 KOA 组和 PMOP 组血清 IL－1β 浓度均高于空白组（$P = 0.023$, $P = 0.003$, $P = 0.006$; $P = 0.013$, $P = 0.006$, $P = 0.003$）。见表 8。

表 5 3 组大鼠造模后不同时点血清 PⅠCP 浓度比较 $\bar{x} \pm s$,ng · mL$^{-1}$

| 组别 | 样本量(只) | 造模后 7 d | 造模后 28 d | 造模后 56 d |
|---|---|---|---|---|
| 空白组 | 6 | 6.958 ± 0.091 | 6.798 ± 0.294 | 6.962 ± 0.183 |
| KOA 组 | 6 | 3.227 ± 0.108 | 2.625 ± 0.070 | 2.660 ± 0.070 |
| PMOP 组 | 6 | 4.602 ± 0.061 | 2.823 ± 0.107 | 2.578 ± 0.053 |
| *F* 值 | | 1 361.136 | 486.723 | 1 374.782 |
| *P* 值 | | 0.000 | 0.000 | 0.000 |

表 6 3 组大鼠造模后不同时点血清 CTX－Ⅰ浓度比较 $\bar{x} \pm s$,ng · mL$^{-1}$

| 组别 | 样本量(只) | 造模后 7 d | 造模后 28 d | 造模后 56 d |
|---|---|---|---|---|
| 空白组 | 6 | 3538.388 ± 41.425 | 3456.483 ± 20.175 | 3516.567 ± 24.757 |
| KOA 组 | 6 | 4028.697 ± 71.704 | 4493.300 ± 55.740 | 4568.928 ± 13.727 |
| PMOP 组 | 6 | 4012.455 ± 36.410 | 4361.232 ± 65.589 | 4343.918 ± 65.111 |
| *F* 值 | | 85.311 | 366.754 | 548.315 |
| *P* 值 | | 0.000 | 0.000 | 0.000 |

表 7 3 组大鼠造模后不同时点血清 NTX－Ⅰ浓度比较 $\bar{x} \pm s$,ng · mL$^{-1}$

| 组别 | 样本量(只) | 造模后 7 d | 造模后 28 d | 造模后 56 d |
|---|---|---|---|---|
| 空白组 | 6 | 5.715 ± 0.288 | 5.837 ± 0.098 | 5.771 ± 0.345 |
| KOA 组 | 6 | 10.696 ± 0.436 | 10.695 ± 0.388 | 7.661 ± 0.672 |
| PMOP 组 | 6 | 10.562 ± 0.530 | 10.073 ± 0.114 | 9.933 ± 0.190 |
| *F* 值 | | 130.859 | 363.652 | 64.452 |
| *P* 值 | | 0.000 | 0.000 | 0.000 |

表 8 3 组大鼠造模后不同时点血清 IL－1β 浓度比较 $\bar{x} \pm s$,ng · mL$^{-1}$

| 组别 | 样本量(只) | 造模后 7 d | 造模后 28 d | 造模后 56 d |
|---|---|---|---|---|
| 空白组 | 6 | 80.623 ± 1.411 | 79.680 ± 0.746 | 80.541 ± 2.307 |
| KOA 组 | 6 | 117.013 ± 3.208 | 133.761 ± 1.858 | 136.367 ± 0.878 |
| PMOP 组 | 6 | 83.680 ± 1.738 | 125.757 ± 3.117 | 129.540 ± 3.830 |
| *F* 值 | | 239.609 | 737.740 | 1 230.488 |
| *P* 值 | | 0.000 | 0.000 | 0.000 |

造模后 7、28、56 d 时各组大鼠血清 IL－6 浓度比较,差异均有统计学意义。造模后各时点 KOA 组血清 IL－6 浓度均高于空白组($P=0.026$,$P=0.003$,$P=0.000$)。造模后 7 d 时 PMOP 组血清 IL－6 浓度与空白组比较,差异无统计学意义($P=0.068$);造模后 28、56 d 时 PMOP 组血清 IL－6 浓度均高于空白组($P=0.023$,$P=0.006$)。见表 9。

造模后 7、28、56 d 时各组大鼠血清 IL－8 浓度比较,差异均有统计学意义。造模后各时点 KOA 组和 PMOP 组血清 IL－8 浓度均高于空白组($P=0.000$,$P=0.000$,$P=0.000$;$P=0.008$,$P=0.000$,$P=0.000$)。见表 10。

造模后 7、28、56 d 时各组大鼠血清 IL－10 浓度比较,差异均有统计学意义。造模后各时点 KOA 组和 PMOP 组血清 IL－10 浓度均低于空白组($P=0.032$,$P=0.029$,$P=0.013$;$P=0.010$,$P=0.000$,$P=0.000$)。见表 11。

造模后 7、28、56 d 时各组大鼠血清 TNF－α 浓度比较,差异均有统计学意义。造模后各时点 KOA 组和 PMOP 组血清 TNF－α 浓度均高于空白组($P=0.000$,$P=0.000$,$P=0.009$;$P=0.000$,$P=0.016$,$P=0.006$)。见表 12。

造模后 7、28、56 d 时各组大鼠血清 MMP－9 浓度比较,差异均有统计学意义。造模后各时点 KOA 组和 PMOP 组血清 MMP－9 浓度均高于空白组($P=0.000$,$P=0.021$,$P=0.002$;$P=0.002$,$P=0.018$,$P=0.000$)。见表 13。

造模后 7、28、56 d 各组大鼠血清 MMP－13 浓度比较,差异均有统计学意义。造模后各时点 KOA 组和 PMOP 组血清 MMP－13 浓度均高于空白组($P=0.000$,$P=0.000$,$P=0.000$;$P=0.000$,$P=0.010$,$P=0.000$)。见表 14。

**表 9　3 组大鼠造模后不同时点血清 IL－6 浓度比较**　$\bar{x}\pm s$,ng·L$^{-1}$

| 组别 | 样本量(只) | 造模后 7 d | 造模后 28 d | 造模后 56 d |
|---|---|---|---|---|
| 空白组 | 6 | 15.398±0.031 | 15.238±0.010 | 15.243±0.006 |
| KOA 组 | 6 | 24.565±0.046 | 24.565±0.023 | 26.427±0.047 |
| PMOP 组 | 6 | 17.878±1.019 | 26.947±0.038 | 27.055±1.539 |
| *F* 值 | | 194.386 | 1 687.916 | 167.754 |
| *P* 值 | | 0.000 | 0.000 | 0.000 |

**表 10　3 组大鼠造模后不同时点血清 IL－8 浓度比较**　$\bar{x}\pm s$,ng·L$^{-1}$

| 组别 | 样本量(只) | 造模后 7 d | 造模后 28 d | 造模后 56 d |
|---|---|---|---|---|
| 空白组 | 6 | 74.540±3.033 | 73.013±1.977 | 75.840±1.794 |
| KOA 组 | 6 | 132.222±4.977 | 128.427±1.845 | 126.642±4.862 |
| PMOP 组 | 6 | 82.075±1.149 | 106.193±3.254 | 118.995±5.280 |
| *F* 值 | | 250.713 | 391.058 | 123.373 |
| *P* 值 | | 0.000 | 0.000 | 0.000 |

**表 11　3 组大鼠造模后不同时点血清 IL－10 浓度比较**　$\bar{x}\pm s$,ng·L$^{-1}$

| 组别 | 样本量(只) | 造模后 7 d | 造模后 28 d | 造模后 56 d |
|---|---|---|---|---|
| 空白组 | 6 | 14.513±0.734 | 14.323±1.986 | 14.093±3.358 |
| KOA 组 | 6 | 6.250±0.802 | 7.307±0.843 | 6.048±1.427 |
| PMOP 组 | 6 | 8.593±0.625 | 9.307±1.860 | 7.335±2.963 |
| *F* 值 | | 105.658 | 14.491 | 7.606 |
| *P* 值 | | 0.000 | 0.005 | 0.023 |

**表 12　3 组大鼠造模后不同时点血清 TNF－α 浓度比较**　$\bar{x}\pm s$,ng·L$^{-1}$

| 组别 | 样本量(只) | 造模后 7 d | 造模后 28 d | 造模后 56 d |
|---|---|---|---|---|
| 空白组 | 6 | 1.345±0.071 | 1.378±0.053 | 1.303±0.042 |
| KOA 组 | 6 | 2.265±0.069 | 2.524±0.063 | 2.647±0.039 |
| PMOP 组 | 6 | 2.371±0.097 | 2.578±0.044 | 2.544±0.039 |
| *F* 值 | | 149.276 | 471.095 | 1 043.479 |
| *P* 值 | | 0.000 | 0.000 | 0.000 |

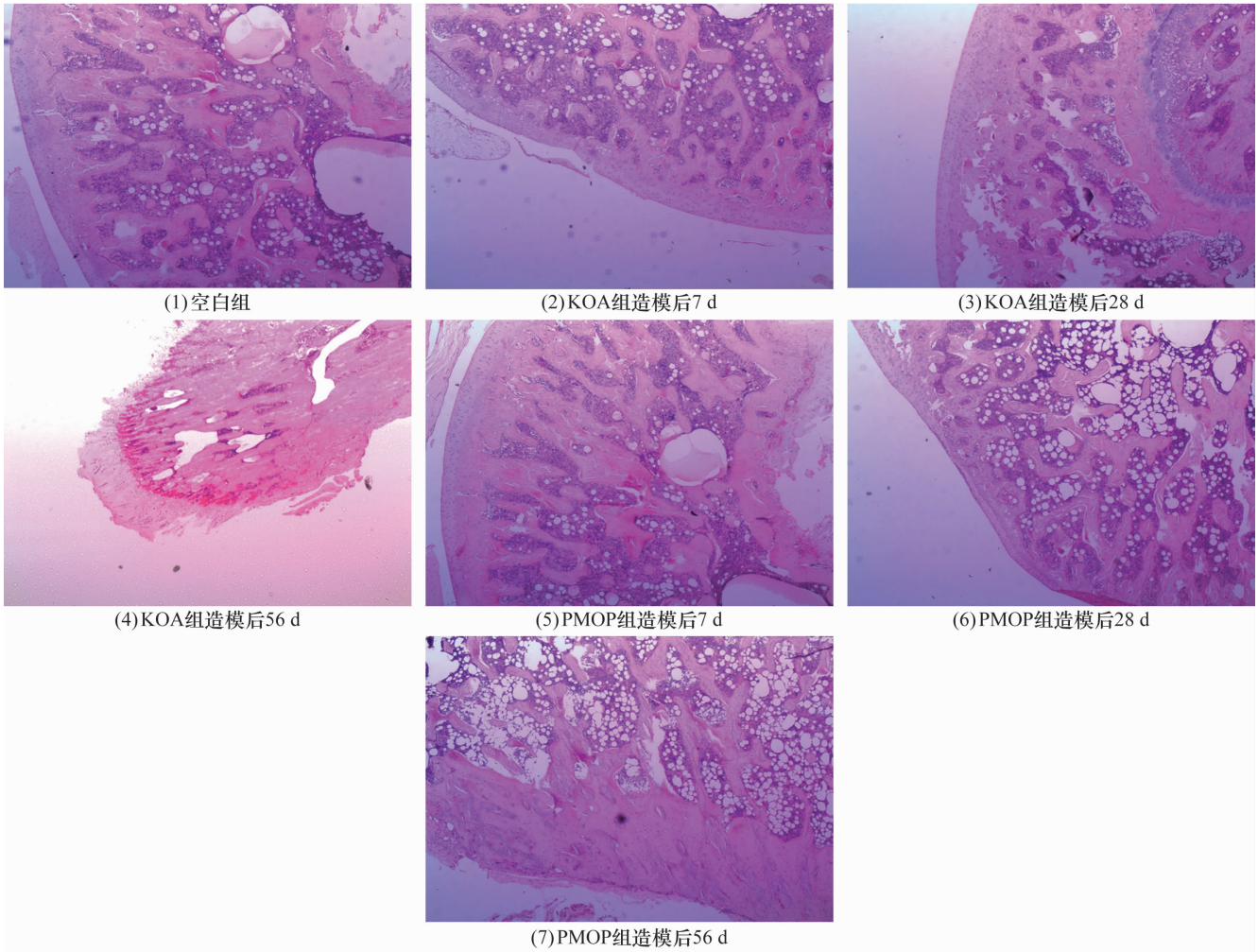
表 13　3 组大鼠造模后不同时点血清 MMP－9 浓度比较　$\bar{x} \pm s$,ng · mL$^{-1}$

| 组别 | 样本量(只) | 造模后 7 d | 造模后 28 d | 造模后 56 d |
|---|---|---|---|---|
| 空白组 | 6 | 14.558 ± 1.353 | 14.855 ± 0.275 | 14.560 ± 0.370 |
| KOA 组 | 6 | 20.707 ± 0.497 | 20.640 ± 1.105 | 25.065 ± 0.285 |
| PMOP 组 | 6 | 18.565 ± 0.220 | 18.788 ± 0.581 | 26.732 ± 0.958 |
| *F* 值 | | 41.242 | 48.075 | 345.274 |
| *P* 值 | | 0.000 | 0.000 | 0.000 |

表 14　3 组大鼠造模后不同时点血清 MMP－13 浓度比较　$\bar{x} \pm s$,ng · mL$^{-1}$

| 组别 | 样本量(只) | 造模后 7 d | 造模后 28 d | 造模后 56 d |
|---|---|---|---|---|
| 空白组 | 6 | 18.917 ± 0.232 | 19.658 ± 0.048 | 19.517 ± 0.048 |
| KOA 组 | 6 | 24.155 ± 0.110 | 33.277 ± 0.068 | 33.077 ± 0.068 |
| PMOP 组 | 6 | 22.155 ± 0.110 | 33.366 ± 0.203 | 33.365 ± 0.101 |
| *F* 值 | | 806.718 | 1 161.386 | 3 292.695 |
| *P* 值 | | 0.000 | 0.000 | 0.000 |

空白组大鼠软骨下骨小梁结构正常，骨皮质致密均一；软骨表面平滑整齐，软骨细胞整齐排列，四层结构分层规则，染色分布均匀，潮线清晰完整。KOA 组造模后 7 d 时软骨下骨小梁略变薄、结构疏松，至造模后 56 d 时软骨下骨小梁有明显的结构紊乱、异构、增生、硬化现象；造模后 7 d 时关节软骨表面平滑整齐，可见细小裂隙及缺损，软骨细胞略紊乱，但四层结构分层仍较规则、潮线清晰完整；至造模后 28、56 d 时软骨表面缺损、裂隙形成，向下延伸达辐射层，分层不清晰，结构不规则，潮线破坏，钙化层明显增厚。PMOP 组造模后 28 d 时软骨下骨小梁稀疏、变细，至造模后 56 d 时可见骨小梁稀疏不连续、间距增大，关节软骨表面出现表浅裂隙、不甚光滑、潮线连续性局部破坏、软骨细胞数量减少。见图 1。



(1)空白组　(2)KOA组造模后7 d　(3)KOA组造模后28 d

(4)KOA组造模后56 d　(5)PMOP组造模后7 d　(6)PMOP组造模后28 d

(7)PMOP组造模后56 d

图 1　3 组大鼠膝关节软骨组织病理切片(HE 染色　×400)

3 组大鼠造模后 7、28、56 d 时膝关节软骨 Mankin's评分比较,组间差异均有统计学意义。造模后各时点 KOA 组关节软骨 Mankin's 评分均高于空白组($P=0.000$,$P=0.000$,$P=0.000$);造模后 7、28 d时,PMOP 组 Mankin's 评分与空白组比较,差异均无统计学意义($P=0.082$,$P=0.056$),造模后 56 d 时 PMOP 组 Mankin's 评分高于空白组($P=0.043$)。见表 15。

**表 15　3 组大鼠造模后不同时点膝关节软骨 Mankin's 评分比较　$\bar{x}\pm s$,分**

| 组别 | 样本量(只) | 造模后 7 d | 造模后 28 d | 造模后 56 d |
|---|---|---|---|---|
| 空白组 | 6 | 0.349 ± 0.113 | 0.583 ± 0.102 | 0.784 ± 0.082 |
| KOA 组 | 6 | 1.335 ± 0.174 | 3.004 ± 0.413 | 4.108 ± 0.643 |
| PMOP 组 | 6 | 0.288 ± 0.105 | 0.374 ± 0.137 | 2.103 ± 0.307 |
| *F* 值 | | 17.348 | 48.643 | 36.582 |
| *P* 值 | | 0.000 | 0.000 | 0.000 |

## 4　讨　论

老年性 OP 主要是由全身性的机能下降所导致,如随着机体肾功能生理性衰退,1,25(OH)2D3 生成减少、甲状旁腺激素分泌增加,导致老年患者骨量下降。而 PMOP 则与女性绝经后卵巢功能下降、雌激素缺乏相关[14-16]。既往对 KOA 发病机制的研究,关注点多为软骨破坏和滑膜炎症,但随着计算机断层扫描技术的进步,有研究者发现 KOA 在尚未出现影像症状的早期即已存在软骨下骨量丢失[17]。软骨下骨的结构完整对关节软骨形态、功能维持有直接影响[18-19]。此外,越来越多的证据表明,除了关节液,软骨下骨也是关节软骨重要的营养来源[20]。因此,一旦软骨下骨发生代谢异常,就可能诱发软骨破坏[21]。

TRACP-5b、BALP、PⅠNP、PⅠCP、CTX-Ⅰ、NTX-Ⅰ均为反映骨代谢的标记物。TRACP-5b 主要由破骨细胞释放,可增加破骨细胞活性[22-23]。BALP 是成骨细胞成熟和具有活性的标志,被认为是最精确的骨形成标志物[24-25]。PⅠNP 和 PⅠCP 是Ⅰ型前胶原经酶切修饰后产生,二者在血清中的含量可反映成骨细胞合成骨胶原的能力,检测骨量变化的特异性和敏感性均非常高[26-27]。CTX-Ⅰ和 NTX-Ⅰ是使用最广泛的胶原降解标志物,其在血清中的含量水平能精确反映破骨细胞的活性[28-30]。IL-1β、IL-6、IL-8、IL-10、TNF-α 作为促炎性细胞因子,在 KOA 及其他炎性疾病的研究中常被作为监测炎性反应的血清学指标,而 MMP-9 和 MMP-13 则是关节软骨基质降解的重要推动酶类,其在血清中的水平可反映 KOA 病理环节中软骨破坏的程度[29]。

从骨密度和血清中 TRACP-5b、BALP、PⅠNP、PⅠCP、CTX-Ⅰ、NTX-Ⅰ含量来看,在 KOA 组大鼠造模后 7、28 d 时存在与着 PMOP 类似的"高转换型"骨代谢紊乱,但到造模后 56 d 时这一趋势有所减缓,而且 KOA 组的这种"高转换型"骨代谢紊乱发生在关节软骨出现明显的病理改变之前,与可监测到的血清炎性指标几乎同步发生,提示 KOA 病程中骨转换速率的加快在 KOA 极早期即已出现。伴随 KOA 病程进展血清炎性指标水平的逐步回落则可能与软骨下骨重建的负反馈调节等因素有关,我们的后续实验正在跟进研究。PMOP 组的"高转换型"骨代谢紊乱持续发生,且有随病程进展加剧的趋势。PMOP 组大鼠在造模后随着病程进展也出现了类似 KOA 的炎症指标异常和关节软骨的组织病理改变,提示高转换型骨代谢或可作为 KOA 一个独立的危险因素。

KOA 属中医学"膝痹""骨痹"范畴,而 PMOP 则可归属于中医学"骨痿""痿证"范畴。"膝痹"病位在膝,膝为筋府,为肝所主;"骨痿"病位在"骨",为肾脏所主。中医理论认为肝肾两脏关系密切,有"肝肾同源"之说,养血柔肝、舒筋活络一直都是膝痹的重要治法之一;而补益肝肾、强骨壮筋则是骨痿的主要治法。中医学在采用补益肝肾、滋阴养血法对这 2 种疾病进行异病同治方面的理、法、方、药也均非常成熟。

本研究的结果提示,KOA 从早期开始即存在与 PMOP 类似的高转换型骨代谢紊乱,而 PMOP 中后期也会出现类似 KOA 的软骨退变;高转换型骨代谢紊乱可能在 KOA 和 PMOP 的发病中具有同样重要的作用,这可作为中医学根据"肝肾同源"理论对 KOA 和 PMOP 进行异病同治的实验理论基础。

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