

doi: 10.13241/j.cnki.pmb.2019.10.022

## 老年慢性阻塞性肺疾病患者营养状况及血清甲状腺素和瘦素表达变化及其相关性分析\*

方江<sup>1</sup> 艾红艳<sup>1</sup> 秦永刚<sup>1</sup> 戢太兵<sup>1</sup> 马红玲<sup>2</sup> 宁立芬<sup>2</sup>

(1 武汉科技大学附属武汉市汉阳医院呼吸内科 湖北 武汉 430050;

2 武汉科技大学附属武汉市汉阳医院检验科 湖北 武汉 430050)

**摘要 目的:**探讨老年慢性阻塞性肺疾病(COPD)患者的营养状况以及血清甲状腺素、瘦素水平变化,并分析其相关性。**方法:**选择我院 2015 年 6 月至 2017 年 12 月收治的 64 例老年 COPD 患者作为研究对象,按照营养状态分为营养不良组(34 例)和非营养不良组(30 例)两组,并选择同期来院检查的 32 例健康人作为对照组,比较三组患者的营养状况以及血清甲状腺素、瘦素水平,并分析血清瘦素水平与营养状况以及血清甲状腺素的相关性。**结果:**营养不良组患者的体重、体质质量(BMI)、血清清蛋白(ALB)、血红蛋白(Hb)、肩胛下皮褶厚度(SSF)、三头肌皮褶厚度(TSF)、上臂周径(MAC)、上臂肌围长(MAMC)、理想体质质量百分比(IBW%)营养状态指标以及血清瘦素、三碘甲状腺原氨酸(T<sub>3</sub>)、四碘甲状腺原氨酸(T<sub>4</sub>)、促甲状腺素(TSH)水平明显低于对照组和非营养不良组,差异具有统计学意义( $P<0.05$ ),而非营养不良组和对照组两组患者的各项营养状态指标差异无统计学意义( $P>0.05$ )。老年 COPD 患者血清瘦素与 BMI、TSF、MAC、IBW%营养指标以及血清 TSH 水平呈正相关( $P<0.05$ )。**结论:**营养不良的老年 COPD 患者的血清瘦素以及甲状腺素水平明显降低,瘦素与 COPD 患者相关营养状态指标以及 TSH 呈正相关,与甲状腺素通过下丘脑-垂体-甲状腺轴,共同参与机体能量代谢、体质质量以及饮食的调节。

**关键词:**老年;慢性阻塞性肺疾病;营养状态;甲状腺素;瘦素;相关性

**中图分类号:**R563 **文献标识码:**A **文章编号:**1673-6273(2019)10-1912-04

## Analysis of Nutritional Status and Serum Thyroid Hormone and Leptin Expression in Elderly Patients with Chronic Obstructive Pulmonary Disease and Their Correlation\*

FANG Jiang<sup>1</sup>, AI Hong-yan<sup>1</sup>, QIN Yong-gang<sup>1</sup>, JI Tai-bing<sup>1</sup>, MA Hong-ling<sup>2</sup>, NING Li-fen<sup>2</sup>

(1 Department of Respiratory Medicine, Wuhan Hanyang Hospital Affiliated to Wuhan University of Science and Technology,

Wuhan, Hubei, 430050, China; 2 Department of Clinical Laboratory,

Wuhan Hanyang Hospital Affiliated to Wuhan University of Science and Technology, Wuhan, Hubei, 430050, China)

**ABSTRACT Objective:** To investigate the nutritional status and serum thyroid hormone and leptin levels in elderly patients with chronic obstructive pulmonary disease (COPD), and to analyze their correlation. **Methods:** Sixty-four elderly patients with COPD, who were admitted to Wuhan Hanyang Hospital Affiliated to Wuhan University of Science and Technology from June 2015 to December 2017 were chosen as study subjects. According to nutritional status, the patients were divided into malnutrition group (34 cases) and non-malnutrition group (30 cases). In the same period, 32 healthy elderly individuals, who came to the hospital for examination, were chosen as control group. The nutritional status and serum thyroid hormone and leptin levels in the three groups were compared. The correlation among serum leptin levels, nutritional status, and serum thyroxine levels was also analyzed. **Results:** The body weight, BMI, ALB, HB, SSF, TSF, MAC, MAMC, IBW% nutritional status indicators and serum leptin, T<sub>3</sub>, T<sub>4</sub>, and TSH levels in the malnourished group were significantly lower than those in the control group and the non-malnutrition group, the difference was statistically significant ( $P<0.05$ ). There was no significant difference in the nutritional status indicators between the non-malnutrition group and the control group ( $P>0.05$ ). Serum leptin levels in elderly COPD patients were positively correlated with BMI, TSF, MAC, IBW% nutritional indicators, and serum TSH levels ( $P<0.05$ ). **Conclusions:** Serum leptin and thyroxine levels are significantly reduced in elderly patients with COPD with malnutrition, and leptin is positively correlated with nutritional status indicators and TSH. It interacts with thyroxine through the hypothalamus-pituitary-thyroid axis and participates in the regulation of body energy metabolism, body weight, and diet.

**Key words:** Elderly; COPD; Nutritional status; Thyroid hormone; Leptin; Correlation

**Chinese Library Classification(CLC):** R563 **Document code:** A

**Article ID:** 1673-6273(2019)10-1912-04

\* 基金项目:湖北省卫生计生委科研计划项目(2016KL032)

作者简介:方江(1981-),女,硕士,主治医师,从事慢性阻塞性肺疾病的发病机理和临床治疗方面的研究,E-mail: fangj198101@163.com

(收稿日期:2018-09-23 接受日期:2018-10-19)

## 前言

慢性阻塞性肺病(Chronic obstructive pulmonary disease, COPD)是一种临床上常见的呼吸系统疾病,以血管、气道炎症为主要特征,在多种炎症因子的参与下,造成患者肺实质损害以及小气道的重组,最后形成肺气肿或者慢性支气管炎<sup>[1]</sup>。调查显示,我国 2001-2008 年 COPD 的发病率从 3.5%升至 6.8%,2012 年调查显示其发病率为 9.6%,并随着我国社会经济发展以及消费人口老龄化的加剧,其发病率也在逐年升高<sup>[2]</sup>。世界卫生组织关于疾病负担的有关研究显示,COPD 疾病经济负担将在 2020 年升至全球第 5 位,已发展为重要的公共卫生问题<sup>[3]</sup>。在 COPD 疾病的进展过程中,患者的营养状况会发生不同程度的改变,其中有大概 40%左右的患者会并发营养不良<sup>[4]</sup>。研究显示,营养不良的 COPD 患者会不同程度导致院内感染、呼吸能力下降、免疫功能下降、脱离机械通气困难以及高碳酸血症性呼吸衰竭等不良症状,增加了患者的死亡率<sup>[5]</sup>。人瘦素是通过与相关受体结合,以及中枢系统发挥生理效应的一种肽类激素,是由肥胖基因 ob 经过转录翻译形成的,主要对机体脂肪的合成以及能量的摄入具有一定的抑制功效,另外还可以控制患者食欲,改善机体体脂状况,其可以与相应的细胞因子联合发挥作用,与机体营养状况关系密切<sup>[6]</sup>。甲状腺素是人体重要的内分泌激素,对机体的氧耗、分化以及生长代谢具有重要的调节功效<sup>[7]</sup>。故本文分析老年 COPD 患者的营养状况、血清甲状腺素、瘦素表达变化及其相关性,为老年 COPD 患者的临床诊治提供参考。

## 1 资料与方法

### 1.1 一般资料

选择我院 2015 年 6 月至 2017 年 12 月收治的 64 例老年 COPD 患者作为研究对象,按照营养状态分为营养不良组(34 例)和非营养不良组(30 例)两组,其中营养不良组患者男 23 例,女 11 例,年龄 63-84 岁,平均年龄(73.2±8.5)岁,病程 2.8-8.1 年,平均病程(5.3±1.5)年,吸烟史者 22 例;非营养不良组患者男 21 例,女 9 例,年龄 64-85 岁,平均年龄(72.3±7.9)岁,病程 3.0-8.3 年,平均病程(5.1±1.4)年,吸烟史者 22 例;另选同期来院检查的 32 例健康老年人作为对照组,其中男 22 例,女 10 例,年龄 62-82 岁,平均年龄(72.4±8.1)岁。上述两组老年 COPD 患者均符合相关诊断标准,且两组患者在年龄、性别以及病程等一般资料方面差异不显著( $P>0.05$ ),具有可比性。

### 1.2 诊断以及分组标准

① 诊断标准:根据中华医学会 2013 年推荐的 COPD 诊断标准<sup>[8]</sup>,具体如下:咳嗽,痰液呈现粘液或者浓性;呼吸困难气短;胸闷喘息;体重下降,活动障碍,肌肉萎缩患者;给予支气管舒张剂以后 FEV1/FVC% $<70\%$ 的患者。② 分组标准<sup>[9]</sup>:营养不良组,总淋巴细胞的数量不低于  $1.2 \times 10^9/L$  者;上臂周径(MAC)不低于 24 cm 者;体质指数(BMI)不低于  $20 \text{ kg/cm}^2$ ,同时伴理想体重百分比不小于 90%者;血清蛋白量不少于 26 g/L 者;三头肌皮皱厚度(TSF)不小于 10 mm 者。符合上述 5 项中的 3 项即可。其余的 COPD 患者即为非营养不良组。

### 1.3 纳入和排除标准

纳入标准:① 符合上述诊断标准者,年龄 $>60$ 岁;② 入院前 12 周以内无感冒以及其他相关呼吸道感染性疾病者;③ 近 1 年内 COPD 急性加重发作不超过 1 次;④ 入院前 6 周无糖皮质激素以及抗生素等相关药物服用史者;⑤ 患者及家属同意并积极配合本次研究,并签署知情协议书。排除标准:① 合并有心力衰竭、肿瘤、结缔组织疾病、肺结核等疾病者;② 合并有肝肾以及甲状腺功能异常者;③ 合并有慢性胃肠道疾病等消耗性疾病者;④ 依从性差,中途退出者。

### 1.4 标本收集

嘱咐所有受试患者在前一天晚上 8 点开始禁食,并于第二天清晨,抽取其 5 mL 的肘正中心静脉血,标记,采用 DL-R 型离心机(中国上海),在 3000 rpm 的条件下离心 10 min,取上层血清于  $-20^\circ\text{C}$  冰箱保存,待测。

### 1.5 检测方法

① 采用全自动生化分析仪(美国贝克曼库尔特公司)对患者血红蛋白(Hb)和血清清蛋白(ALB)含量进行测定;② 营养状态指标测定<sup>[10]</sup>:于清晨 8 点左右,所有受试人员免冠、脱鞋、仅着内衣、空腹的条件下,统一进行肩胛下皮褶厚度(SSF)、三头肌皮褶厚度(TSF)、身高、上臂周径(MAC)、腹围、胸围、体质量(BMI)进行测量,而上臂肌围长(MAMC)为  $\text{MAC-TSF} \times 3.14$ ,理想体质量百分比(IBW%)为受试个体体质量 / 理想体质量  $\times 100\%$ , $\text{BMI} = \text{体重} / \text{身高}^2$ 。③ 血清瘦素水平测定<sup>[11]</sup>:通过智能放免  $\gamma$  计数仪(SN-695B 型,中科院上海日环仪器研究所)采用平衡法,根据液相竞争抑制的相关原理进行血清瘦素测定,试剂盒选用人血清瘦素放射免疫分析试剂盒(国药准字 S20083066;潍坊三维生物工程集团有限公司),操作方法严格按照说明书规定。④ 甲状腺素测定<sup>[12]</sup>:采用智能放免  $\gamma$  计数仪,通过竞争性放射免疫分析法对三碘甲状腺原氨酸(T3)、四碘甲状腺原氨酸(T4)测定,促甲状腺素(TSH)采用液相非平衡顺序竞争放射免疫分析法测定,试剂盒选用三碘甲状腺原氨酸以及人血清促甲状腺素放射分析药盒(潍坊三维生物工程集团有限公司)。

### 1.6 统计学分析

采用统计学专用软件 SPSS 20.0 对上述数据进行整理分析,其中计数资料行卡方检验,计量资料采用( $\bar{x} \pm s$ )表示,组间比较采用 t 检验,并采用 Pearson 方法进行相关性分析,当  $P<0.05$  时,数据差异显著,具有统计学意义。

## 2 结果

### 2.1 三组患者营养状态指标比较

营养不良组患者的体重、BMI、ALB、Hb、SSF、TSF、MAC、MAMC 以及 IBW%等各项营养状态指标明显低于对照组和非营养不良组,差异具有统计学意义( $P<0.05$ )。而非营养不良组和对照组两组患者的各项营养状态指标差异无统计学意义( $P>0.05$ )。见表 1。

### 2.2 三组患者血清甲状腺素、瘦素水平比较

营养不良组患者的血清瘦素以及 T3、T4、TSH 甲状腺素水平明显低于对照组和非营养不良组,差异具有统计学意义( $P<0.05$ )。而非营养不良组和对照组两组患者的血清甲状腺素、瘦素水平差异无统计学意义( $P>0.05$ )。见表 2。

表 1 三组患者营养状态指标比较( $\bar{x} \pm s$ )

Table 1 Comparison of nutritional status indicators of three groups of patients ( $\bar{x} \pm s$ )

| Groups                     | Weight (kg) | BMI (kg/cm <sup>2</sup> ) | ALB(g/L)    | Hb(g/L)       | SSF(cm)    | TSF(cm)     | MAC(cm)     | MAMC(cm)    | IBW%       |
|----------------------------|-------------|---------------------------|-------------|---------------|------------|-------------|-------------|-------------|------------|
| Malnourished group (n=34)  | 52.6± 8.7   | 19.0± 1.1                 | 30.4± 2.2   | 129.8± 10.2   | 2.0± 0.3   | 7.8± 2.4    | 20.0± 2.5   | 24.1± 2.7   | 1.0± 0.2   |
| Non-nutrition group (n=30) | 70.2± 9.5*  | 21.6± 1.3*                | 34.9± 3.0*  | 143.9± 11.2*  | 2.5± 0.4*  | 11.0± 3.5*  | 23.8± 3.1*  | 26.8± 2.6*  | 1.4± 0.2*  |
| Control group (n=32)       | 72.1± 9.4** | 22.3± 1.5**               | 35.4± 2.9** | 145.3± 11.6** | 2.6± 0.4** | 11.3± 3.8** | 24.5± 3.3** | 27.3± 2.5** | 1.4± 0.3** |
| F                          | 7.736       | 8.667                     | 6.896       | 5.271         | 5.697      | 4.308       | 5.424       | 4.062       | 7.984      |
| P                          | 0.000       | 0.000                     | 0.000       | 0.000         | 0.000      | 0.000       | 0.000       | 0.000       | 0.000      |

Note: Compared with non-nutrition group, \* $P>0.05$ ; compared with malnourished group, \*\* $P<0.05$ .

表 2 三组患者血清甲状腺素、瘦素水平比较( $\bar{x} \pm s$ )

Table 2 Comparison of serum thyroxine and leptin levels in three groups of patients ( $\bar{x} \pm s$ )

| Groups                     | Leptin (ng/L) | T3(nmol/L) | T4(nmol/L)   | TSH(mU/L)  |
|----------------------------|---------------|------------|--------------|------------|
| Malnourished group (n=34)  | 4.0± 1.6      | 1.3± 0.6   | 60.2± 12.8   | 1.3± 0.4   |
| Non-nutrition group (n=30) | 6.5± 2.3*     | 1.9± 0.4*  | 80.1± 13.6*  | 1.8± 0.3*  |
| Control group (n=32)       | 6.9± 2.7**    | 2.1± 0.3** | 85.2± 16.7** | 1.9± 0.3** |
| F                          | 5.095         | 4.640      | 6.028        | 5.595      |
| P                          | 0.000         | 0.000      | 0.000        | 0.000      |

Note: Compared with non-nutrition group, \* $P>0.05$ ; compared with malnourished group, \*\* $P<0.05$ .

### 2.3 血清瘦素水平与相关营养状态指标和甲状腺素水平的相关性

老年 COPD 患者血清瘦素与 BMI、TSF、MAC、IBW% 营养指标以及血清 TSH 水平呈正相关( $P<0.05$ ),见表 3。

表 3 血清瘦素水平与相关营养状态指标和甲状腺素水平的相关性

Table 3 Correlation among serum leptin levels and related nutritional status indicators and thyroxine levels

| Indexes | r     | P     |
|---------|-------|-------|
| BMI     | 0.854 | 0.039 |
| TSF     | 0.283 | 0.000 |
| MAC     | 0.062 | 0.000 |
| IBW%    | 0.575 | 0.015 |
| TSH     | 0.375 | 0.000 |

## 3 讨论

老年 COPD 患者通常会并发大量的不良反应,增加其病死率<sup>[12]</sup>。研究显示,与同等呼吸力学的正常人相比,低体重 COPD 患者的运动能力以及肺泡氧扩散能力相对较低,进而造成耐力和肌肉力量下降,逐渐使患者身体衰弱,免疫力下降,机体气道的自我防御能力降低<sup>[13,14]</sup>。上述相关因素会直接或者间接的引起院内肺感染、低氧、高碳酸血症性呼吸衰竭等不良反应的发生,其会使 COPD 患者的新陈代谢发生紊乱<sup>[15]</sup>。可能会提高机体的代谢率,恶化营养不良状态<sup>[16]</sup>;感染可能会引发机体肌肉蛋白水解的发生<sup>[17]</sup>;相关激素的治疗可以使肌肉中氨基酸的转入和蛋白质的合成受到有效抑制,促进糖异生以及蛋白质水解<sup>[18]</sup>。由于 COPD 反复发作的特点,糖皮质激素的使用率较高,

蛋白质分解加速,会造成 MAMC 显著低于正常人<sup>[19]</sup>。COPD 患者在处于应激条件下时,脂肪以及碳水化合物的代谢会受到神经内分泌系统的调节,而 SSF、TSF 是反映机体脂肪储备的指标,明显降低<sup>[20]</sup>。

瘦素是一种由白细胞合成的多肽类激素,主要参与患者内分泌、代谢以及饮食等功能的调节,对于平衡机体能量代谢起着重要的作用<sup>[21]</sup>。研究显示,下丘脑是瘦素重要的作用靶点之一,使机体释放和分泌的下丘脑神经肽 Y 含量降低,抑制神经肽的摄食诱导作用,降低食欲<sup>[22]</sup>。其还可以进一步刺激肌肉以及棕色脂肪组织,增强其中去甲状腺素的释放量,再于相应的受体结合,增加去偶联蛋白的合成量,交感神经兴奋,产热增加,提高机体代谢效率<sup>[23,24]</sup>。另外,瘦素对于脂肪的合成还具有一定程度的抑制作用,其是一种负反馈调节,机体脂肪量增加,

分泌的瘦素相对增加,其刺激下丘脑从而抑制患者的食欲,摄入量降低,消耗的体脂增加,反馈调节,降低血清瘦素的分泌量,食欲进一步增加,体脂增加,如此循环调节,而营养不良的COPD患者,代谢紊乱,体质量降低,循环血清瘦素水平降低,瘦素与相关的营养状态指标呈正相关<sup>[25]</sup>。COPD患者会并发大量的炎症反应,白介素-1、肿瘤坏死因子- $\alpha$ 等相关细胞因子生成增加,显著抑制甲状腺素结合蛋白、TSH、T3以及T4合成<sup>[26]</sup>;另外,营养不良的COPD患者,体重减轻,免疫力下降,体质衰弱,肝肾功能减退,致使合成的相关蛋白量降低,甲状腺激素代谢途径障碍,故营养不良组患者的TSH、T3以及T4含量明显较低<sup>[27]</sup>。文中资料显示,血清瘦素水平与TSH含量呈正比,提示机体内部正常生理浓度TSH对于血清瘦素的功能水平维持起着重要作用,两者之间主要通过下丘脑-垂体-甲状腺轴系统进行相互调节,其一方面脂肪细胞中的TSH可以与特异性受体相结合,激活细胞中的CAMP途径,调节脂肪细胞代谢,进而调节瘦素的合成与分泌;另一方面,其还可以在细胞膜上直接发挥作用调节瘦素的合成与分泌<sup>[28,29]</sup>。瘦素和甲状腺素是下丘脑-垂体-甲状腺轴调节系统中重要的两种物质,在脂肪细胞以及下丘脑中发挥相互作用,共同参与机体能量代谢、体质量以及饮食的调节<sup>[30]</sup>。

综上所述,营养不良的老年COPD患者的血清瘦素以及甲状腺素水平明显降低,瘦素与COPD患者相关营养状态指标以及TSH呈正相关,与甲状腺素通过下丘脑-垂体-甲状腺轴,共同参与机体能量代谢、体质量以及饮食的调节。

#### 参考文献(References)

- [1] 杨琼芳,方双燕,季巧英,等.慢性阻塞性肺疾病急性加重合并肺栓塞患者的临床表现和辅助检查特征分析[J].浙江医学,2016,38(22): 1831-1833
- [2] Zeki AA, Jarjour NN. The Asthma-Chronic Obstructive Pulmonary Disease Overlap Syndrome: A New Take on an Old Concept [J]. Ann Am Thorac Soc, 2016, 13(9): 1440-1442
- [3] Guirguis-Blake JM, Senger CA, Webber EM, et al. Screening for Chronic Obstructive Pulmonary Disease: Evidence Report and Systematic Review for the US Preventive Services Task Force [J]. Jama, 2016, 315(13): 1378-1393
- [4] Hogan D, Lan LT, Diep DT, et al. Nutritional status of Vietnamese outpatients with chronic obstructive pulmonary disease [J]. J Hum Nutr Diet, 2016, 30(1): 83-89
- [5] Matkovic Z, Cvetko D, Rahelic D, et al. Nutritional Status of Patients with Chronic Obstructive Pulmonary Disease in Relation to their Physical Performance[J]. COPD, 2017, 14(6): 626-634
- [6] 朱瑞航,余艳芳,屠春林.低分子肝素钠治疗慢性阻塞性肺疾病急性加重期的疗效分析[J].贵州医药,2016,40(5): 484-486
- [7] Mohan A, Sharma M, Uniyal A, et al. Variability in proteinase-antiproteinase balance, nutritional status, and quality of life in stable chronic obstructive pulmonary disease due to tobacco and nontobacco etiology[J]. Lung India, 2016, 33(6): 605-610
- [8] 潘洋,赵玉,张昀.血清脂联素及瘦素与慢性阻塞性肺疾病并发骨质疏松的相关性[J].实用医学杂志,2015,31(23): 3929-3931
- [9] 王治国,石庆学,郭佳,等. COPD患者肺功能与甲状腺激素水平的关联性分析[J].标记免疫分析与临床,2017,24(5): 516-519
- [10] 叶文生,陈仰新,余志辉,等.肺康复治疗对稳定期慢性阻塞性肺疾病患者免疫功能影响的研究 [J]. 白求恩医学杂志,2017,15(3): 345-347
- [11] Akbulut G, Gezmenkaradağ M, Ertaş Y, et al. Plasma orexin-A and ghrelin levels in patients with chronic obstructive pulmonary disease: Interaction with nutritional status and body composition[J]. Exp Ther Med, 2014, 7(6): 1617-1624
- [12] Dhakal N, Lamsal M, Baral N, et al. Oxidative stress and nutritional status in chronic obstructive pulmonary disease [J]. J Clin Diagn Res, 2015, 9(2): 1-4
- [13] Durheim MT, Cyr DD, Lopes RD, et al. Chronic obstructive pulmonary disease in patients with atrial fibrillation: Insights from the ARISTOTLE trial[J]. Int J Cardiol, 2016, 202(5): 589-594
- [14] 黄国兰,杨卫红,蒲柳美.2型糖尿病合并慢性阻塞性肺疾病患者血清瘦素水平的变化及其临床意义 [J]. 现代医学,2017,53(5): 721-725
- [15] Mutlu L C, Altintas N, Aydin M, et al. Growth Differentiation Factor-15 Is a Novel Biomarker Predicting Acute Exacerbation of Chronic Obstructive Pulmonary Disease [J]. Inflammation, 2015, 38(5): 1805-1813
- [16] 徐春燕,郭水根,沈瑶.老年慢性阻塞性肺疾病急性加重期甲状腺激素水平及影响因素分析[J].老年医学与保健,2017,23(4): 341-343
- [17] Watz H, Tetzlaff K, Wouters EF, et al. Blood eosinophil count and exacerbations in severe chronic obstructive pulmonary disease after withdrawal of inhaled corticosteroids: a post-hoc analysis of the WISDOM trial[J]. Lancet Respir Med, 2016, 4(5): 390-398
- [18] Mcivor RA, Tashkin DP. Underdiagnosis of chronic obstructive pulmonary disease: a rationale for spirometry as a screening tool[J]. Can Respir J, 2016, 8(3): 153-162
- [19] Vestbo J, Anderson JA, Brook RD, et al. Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk (SUMMIT): a double-blind randomised controlled trial[J]. Lancet, 2016, 387(10030): 1817-1826
- [20] van der Palen J, Klein JJ, Kerkhoff AH, et al. Evaluation of the effectiveness of four different inhalers in patients with chronic obstructive pulmonary disease[J]. Thorax, 1995, 50(11): 1183-1187
- [21] Huiart L, Ernst P, Ranouil X, et al. Oral corticosteroid use and the risk of acute myocardial infarction in chronic obstructive pulmonary disease[J]. Can Respir J, 2006, 13(3): 134-138
- [22] Tulek B, Kivrak AS, Ozbek S, et al. Phenotyping of chronic obstructive pulmonary disease using the modified Bhalla scoring system for high-resolution computed tomography [J]. Can Respir J, 2013, 20(2): 91-96
- [23] Sin DD, Tu JV. Outpatient antibiotic therapy and short term mortality in elderly patients with chronic obstructive pulmonary disease[J]. Can Respir J, 2000, 7(6): 466-475
- [24] van Eeden SF, Sin DD. Oxidative stress in chronic obstructive pulmonary disease: A lung and systemic process [J]. Can Respir J, 2013, 20(1): 27-29
- [25] Khaefi M, Geravandi S, Hassani G, et al. Association of Particulate Matter Impact on Prevalence of Chronic Obstructive Pulmonary Disease in Ahvaz, Southwest Iran during 2009-2013 [J]. Aerosol & Air Quality Research, 2017, 17(1): 1-8

- analyses of area fraction of different ratios of Bio-Oss and bone prior to grafting procedures - An in vitro study to demonstrate a baseline[J]. Clin Oral Implants Res, 2018, 29(2): 185-191
- [9] Aludden HC, Mordenfeld A, Hallman M, et al. Lateral ridge augmentation with Bio-Oss alone or Bio-Oss mixed with particulate autogenous bone graft: a systematic review [J]. Int J Oral Maxillofac Surg, 2017, 46(8): 1030-1038
- [10] 董露,肖琼,杨琴秋,等.富血小板纤维蛋白与胶原膜修复牙龈缺损创面的能力[J].中国组织工程研究, 2016, 20(16): 2340-2346
- [11] Tehrani A, Behnia H, Pourdanesh F, et al. The effect of autologous leukocyte platelet rich fibrin on the rate of orthodontic tooth movement: A prospective randomized clinical trial [J]. Eur J Dent, 2018, 12(3): 350-357
- [12] Ibraheem W. Effect of Platelet-rich Fibrin and Free Gingival Graft in the Treatment of Soft Tissue Defect preceding Implant Placement[J]. J Contemp Dent Pract, 2018, 19(7): 895-899
- [13] 毛俊丽,王拓,孙勇,等.PRF 的制备及保存方法的研究进展[J].西南国防医药, 2016, 26(3): 326-327
- [14] Liu Z, Li C, Zhou J, et al. Endoscopically controlled flapless transcrestal sinus floor elevation with platelet-rich fibrin followed by simultaneous dental implant placement: A case report and literature review[J]. Medicine (Baltimore), 2018, 97(17): e0608
- [15] Maharjan A, Regmi S, Sagtani RA. Knowledge and Awareness Regarding Dental Implants among Patients Attending a Tertiary Care Center[J]. JNMA J Nepal Med Assoc, 2018, 56(210): 578-581
- [16] Oancea C, Luu A, Ambrožová I, et al. Perturbations of radiation field caused by titanium dental implants in pencil proton beam therapy[J]. Phys Med Biol, 2018, 63(21): 215020
- [17] Tallarico M, Caneva M, Baldini N, et al. Patient-centered rehabilitation of single, partial, and complete edentulism with cemented- or screw-retained fixed dental prosthesis: The First Osstem Advanced Dental Implant Research and Education Center Consensus Conference 2017[J]. Eur J Dent, 2018, 12(4): 617-626
- [18] Pichotano EC, de Molon RS, Freitas de Paula LG, et al. Early Placement of Dental Implants in Maxillary Sinus Grafted With Leukocyte and Platelet-Rich Fibrin and Deproteinized Bovine Bone Mineral[J]. J Oral Implantol, 2018, 44(3): 199-206
- [19] Diana C, Mohanty S, Chaudhary Z, et al. Does platelet-rich fibrin have a role in osseointegration of immediate implants A randomized, single-blind, controlled clinical trial [J]. Int J Oral Maxillofac Surg, 2018, 47(9): 1178-1188
- [20] Chenchev IL, Ivanova VV, Neychev DZ, et al. Application of Platelet-Rich Fibrin and Injectable Platelet-Rich Fibrin in Combination of Bone Substitute Material for Alveolar Ridge Augmentation - a Case Report[J]. Folia Med (Plovdiv), 2017, 59(3): 362-366
- [21] Khan ZA, Jhingran R, Bains VK, et al. Evaluation of peri-implant tissues around nanopore surface implants with or without platelet rich fibrin: a clinico-radiographic study [J]. Biomed Mater, 2018, 13(2): 025002
- [22] Shah R, M G T, Thomas R, et al. An Update on the Protocols and Biologic Actions of Platelet Rich Fibrin in Dentistry [J]. Eur J Prosthodont Restor Dent, 2017, 25(2): 64-72
- [23] S Medikeri R, Meharwade V, M Wate P, et al. Effect of PRF and Allograft Use on Immediate Implants at Extraction Sockets with Periapical Infection -Clinical and Cone Beam CT Findings [J]. Bull Tokyo Dent Coll, 2018, 59(2): 97-109
- [24] 王拓,杨琴秋,董露,等.富血小板纤维蛋白诱导口腔缺损软组织的修复与再生[J].中国组织工程研究, 2016, 20(07): 957-965
- [25] 衣红梅,薛洪权,吴鸿,等.富含血小板纤维蛋白修复即刻种植体周围骨缺损的临床观察[J].现代口腔医学杂志, 2018, 32(1): 20-22
- [26] Zhou WL, Li LL, Qiu XR, et al. Effects of Combining Insulin-like Growth Factor 1 and Platelet-derived Growth Factor on Osteogenesis around Dental Implants[J]. Chin J Dent Res, 2017, 20(2): 105-109
- [27] Kong XQ, Huang YX, Li JL, et al. Prognostic value of vascular endothelial growth factor receptor 1 and class III  $\beta$ -tubulin in survival for non-metastatic rectal cancer[J]. World J Gastrointest Oncol, 2018, 10(10): 351-359
- [28] Zhang ZH, Miao YY, Ke BL, et al. LY2109761, Transforming Growth Factor  $\beta$  Receptor Type I and Type II Dual Inhibitor, is a Novel Approach to Suppress Endothelial Mesenchymal Transformation in Human Corneal Endothelial Cells [J]. Cell Physiol Biochem, 2018, 50(3): 963-972
- [29] Clark D, Rajendran Y, Paydar S, et al. Advanced platelet-rich fibrin and freeze-dried bone allograft for ridge preservation: A randomized controlled clinical trial[J]. J Periodontol, 2018, 89(4): 379-387
- [30] Cortellini S, Castro AB, Temmerman A, et al. Leucocyte-and platelet-rich fibrin block for bone augmentation procedure: A proof-of-concept study[J]. J Clin Periodontol, 2018, 45(5): 624-634
- 
- (上接第 1915 页)
- [26] Hobbs BD, Jong KD, Lamontagne M, et al. Genetic loci associated with chronic obstructive pulmonary disease overlap with loci for lung function and pulmonary fibrosis[J]. Nat Genet, 2017, 49(3): 426-432
- [27] Au DH. Screening for Chronic Obstructive Pulmonary Disease: D Is the New F[J]. JAMA Intern Med, 2016, 176(5): 1372-1377
- [28] Lacasse Y, Daigle JM, Martin S, et al. Validity of chronic obstructive pulmonary disease diagnoses in a large administrative database [J]. Can Respir J, 2016, 19(2): e5-e12
- [29] Rowe BH, Cydulka RK, Tsai CL, et al. Comparison of Canadian versus United States emergency department visits for chronic obstructive pulmonary disease exacerbation[J]. Can Respir J, 2016, 15(6): 295-395
- [30] Marciniuk DD, Brooks D, Butcher S, et al. Optimizing pulmonary rehabilitation in chronic obstructive pulmonary disease--practical issues: a Canadian Thoracic Society Clinical Practice Guideline [J]. Can Respir J, 2016, 17(4): 159-168