·综述·

垂体促性腺激素水平变化及对老年病的影响

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【摘 要】 促性腺激素卵泡刺激素(FSH)和黄体生成素(LH)是垂体细胞合成、分泌的多功能激素,除影响生殖系统外,还具有多重生理功能,参与老化相关疾病的发生与发展。随年龄增长,中枢神经垂体功能减退,FSH、LH合成与分泌随之发生变化,这种变化与动脉硬化性心血管疾病、代谢异常等老化相关疾病关系密切,调节FSH、LH可能成为相关疾病防治的重要环节。目前,其确切病理生理作用还不完全清楚,因此深入研究中枢神经系统功能变化与老化相关疾病的关系具有重要意义。

【关键词】 卵泡刺激素;黄体生成素;老化;骨质疏松;动脉硬化性心血管病;代谢异常
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Effect of changes of pituitary gonadotropin level on senile diseases

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【Abstract】 The gonadotrophin hormones, follicle-stimulating hormone (FSH) and luteinizing hormone (LH), are multifunctional hormones synthesized and secreted by pituitary cells. In addition to affecting the reproductive system, they also have multiple physiological functions and participate in the occurrence and development of aging-related diseases. Elevated LH and FSH levels implicated with the decline of pituitary gonadotrope cells during aging process, and recent research data indicated that these changes involve with development of many aged-related chronic diseases, such as atherosclerotic cardiovascular disease, metabolic disturbers, and others. Regulating FSH and LH may become an important link in the prevention and treatment of related diseases. At present, the underlying mechanisms for them remain elusive or largely unknown. Hence, further studies on the relation between central nerve system function and aged-related diseases are of valuable clinical significance.

【Key words】 follicle-stimulating hormone; luteinizing hormone; ageing; osteoporosis; atherosclerotic cardiovascular disease; metabolic disturbers

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垂体促性腺激素卵泡刺激素(follicle-stimulating hormone,FSH)和黄体生成素(luteinizing hormone,LH)除对哺乳动物生殖系统发育和功能发挥关键作用外,还具有多种生物学功能[1,2]。FSH、LH随年龄变化,与动脉硬化、动脉硬化性心血管疾病(atherosclerotic cardiovascular disease,ASCVD)、炎症、胰岛素抵抗、脂肪细胞重排、肥胖、活性氧形成、骨质疏松、认知功能减退等疾病及老化病理生理状态关系密切[3-5],并且可能是这些疾病发生、进展的重要环节,因此日益受到关注。

1 FSH和LH的释放调控与生物学作用

垂体促性腺细胞合成、分泌的FSH、LH为糖蛋白非共价异二聚体,由α-糖蛋白亚单位(α-glycoprotein subunit,αGSU)和β-糖蛋白亚单位(βGSU)组成。FSH和LH的αGSU结构相同,由92氨基酸组成,促性腺细胞可产生大量αGSU,受促性腺激素释放激素(gonadotropin-releasing hormone,GnRH)影响较弱。与αGSU不同,βGSU的FSH-β和LH-β分别由121、109氨基酸组成,因此βGSU转录调控是垂体激素合成的限速环节[2,6,7]。

促性腺激素基因表达调控因素复杂,GnRH对*FSH-β*、*LH-β*基因转录调控最重要。GnRH呈低、高频率波动式释放,分别主要刺激*FSH-β*、FSH及*LH-β*、LH基因表达与蛋白合成。另外,丝裂元活化蛋白激酶(mitogen-activated protein kinase,MAPK)、

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Ca^{2+}动员、T细胞活化核因子(nuclear factor of activated T-cells,NFAT)、蛋白激酶A(protein kinase A,PKA)信号途径参与βGSU转录调控[2,7]。

正常状态下,机体通过下丘脑-垂体-性腺轴(hypothalamic-pituitary-gonadal axis)调控FSH和LH分泌。下丘脑神经元合成的十肽GnRH与垂体促性腺细胞GnRH受体(GnRH receptor,GnRHR)特异性结合,调控垂体促性腺细胞产生、分泌FSH和LH;FSH呈构成式释放,而LH储存于分泌颗粒中,通过GnRH波动变化调控释放;FSH和LH激活性腺释放固醇激素通过反馈抑制下丘脑分泌GnRH,影响促性腺激素的合成[2,6,7]。女性绝经后性激素降低使反馈性抑制减弱,FSH、LH浓度显著升高[8]。

促性腺激素分别通过靶组织卵泡刺激素受体(follicle-stimulating hormone receptor,FSHR)、黄体生成素受体(luteinizing hormone receptor,LHR)发挥生物学作用。FSHR和LHR组织分布广泛,除胎盘、子宫内膜、睾丸,肿瘤组织外,中枢神经、肺、肝、脾、肾脏、心肌细胞、血管内皮细胞、单核细胞、淋巴细胞、骨和脂肪组织均有不同水平的表达。因此,促性腺激素除发挥重要生殖系统影响外,还应具有多重生物学作用,但目前对此尚了解不足[9-11]。

2 年龄相关垂体促性腺细胞及FSH、LH的变化

LH和FSH浓度随年龄增高[3,8,12],女性分别每年升高4.42%、12.76%,男性4.45%、7.11%,女性56~60岁达峰值后浓度稳定,男性缓慢轻度升高,无明显波动。成年女性[(52.87±13.22)岁]LH和FSH浓度较同龄男性[(53.19±13.14岁)]高近5倍[13]。这些变化的原因,除性激素水平降低对HPG轴垂体促性腺激素合成、释放负反馈抑制减弱及性别影响外,垂体促性腺细胞数量、功能变化及局部细胞间互相影响也对LH和FSH的合成与分泌起重要作用。从幼年、成熟到老年,垂体促性腺激素细胞数量及释放FSH和LH量不同[14,15]。迄今,人们对促性腺细胞老化过程组织学研究较少,年龄相关促性腺激素变化的确切机制大多尚待阐明。

垂体前叶LH、FSH合成、分泌主要涉及激素分泌细胞和通过旁分泌/自分泌作用调控前者的支持性胶质样细胞,即卵泡星状细胞(folliculostellate cells,FSC)[15,16]。Čukuranović等[15]对垂体激素分泌细胞做了详尽的总结,垂体促性腺激素分泌细胞有两种分型:(1)按LH、FSH及共表达FSH/LH蛋白表达垂体促性腺细胞可分为三类;(2)根据分泌颗粒大小还可分为Ⅰ、Ⅱ型,Ⅰ型细胞含大颗粒和小颗粒,分泌FSH和LH,Ⅱ型细胞只含小分泌颗粒,分泌LH。年轻、中年雄性大鼠Ⅰ型细胞多于Ⅱ型细胞,但中年鼠垂体表达FSH细胞减少,老年鼠Ⅱ型细胞增多,Ⅰ型细胞减少。上述细胞类型变化可能是老年鼠保持LH浓度稳定不变,FSH浓度显著降低的原因。此外,随年龄增加,大鼠垂体促性腺激素细胞密度、容积密度及表面密度持续降低,年轻和老年鼠促性腺激素细胞周长增加,但高龄鼠细胞周长显著降低,基线血清LH和FSH浓度与细胞周长变化一致。与大鼠有所不同,幼年雄性恒河猴LH/FSH阳性促性腺激素细胞比例显著低于成年,LH及共FSH/LH阳性细胞数量随年龄增加,而FSH表达细胞数量无明显变化[14]。人垂体LH细胞数量相对稳定,随年龄增加变化不明显,临床尸解研究观察到[15],男性从成年到老年(41~87岁)随年龄增加(30~49岁,50~69岁,≥70岁),垂体LH细胞密度无明显变化,但细胞面积显著增加,核浆比降低,特别是≥70岁人群,说明老年男性随年龄增加垂体LH细胞逐渐肥大,细胞功能减退。

3 垂体促性腺激素对骨质疏松的影响

骨质疏松是老年人最常见的骨骼疾病[4]。随年龄增长FSH浓度越高,骨密度(bone mineral density,BMD)越低。高FSH水平女性较低FSH者骨丢失增加1.3~2.3倍。绝经前血清FSH水平>30 IU/L者骨转化标志物浓度显著升高,绝经后妇女血清骨钙素、Ⅰ型胶原C-末端肽水平与FSH正相关[17-19]。

研究表明,小鼠卵巢切除导致骨丢失,而卵巢、垂体同时切除则不发生骨丢失,切除卵巢小鼠敲除FSHR和FSHβ同样不出现骨丢失。LH对骨质影响与FSH相反,成骨细胞表达LHR,敲除LHR小鼠BMD降低[4,17]。FSH可通过FSHR激活抑制型G蛋白$_{2\alpha}$($Gi_{2\alpha}$)及丝裂原激活蛋白激酶(mitogen-activated protein kinase,MAPK)/细胞外调节蛋白激酶(extracellular regulated protein kinases,ErK)、核因子-κB(nuclear factor-κB,NF-κB)及Akt信号促进破骨细胞的生成增加和骨吸收。FSHR表达刺激NFκB表达,FSHR表面表达增加促进炎性因子白介素1β(interleukin 1β,IL-1β)、肿瘤坏死因子-α(TNF-α)及白介

素-6(interleukin 6,IL-6)释放,间接刺激破骨细胞生成。体外实验证明,抑制 FSH 可阻断破骨细胞形成,FSHβ 抗体可通过刺激骨形成、抑制骨吸收,减轻骨丢失。研究还观察到,女性 *FSHR*^{N680S} 基因多态性激活可导致骨吸收增加,骨量下降,而二基因组合,如野生型 *CYP*19A1(芳香化酶)基因 3′非翻译区或 *CYP*19A1 基因标志 IVS4 分别与 *BMP*15、*FSHR* 基因组合发挥骨保护作用[3,4]。

4 垂体促性腺激素与代谢异常及心血管疾病

垂体促性腺激素升高与血糖、血脂、尿酸代谢异常、高血压及 ASCVD 关系密切[5,18]。男性前列腺癌 GnRH 激动剂去雄性激素治疗(androgen deprivation therapy,ADT)升高 FSH,影响心血管功能、促进动脉硬化、增加血栓风险[19]。女性多囊卵巢综合征患者血 LH 浓度显著升高、LH/FSH 降低,颈动脉内中膜厚度(carotid artery intima-media thickness,IMT)显著增加[20]。

与 GnRH 激动剂及阉割动物比较,GnRH 拮抗剂干预可显著降低小鼠 FSH 水平、脂肪量(fat mass),高密度脂蛋白升高、低密度脂蛋白降低,动脉硬化斑块负荷下降至少 2 倍。在 ADT 模型小鼠观察到,FSH 与单核细胞 FSHR 结合上调核因子-κβ 受体活化因子(receptor activator of nuclear factor-κβ,RANK-κβ),促单核细胞侵润动脉硬化斑块,辅助 T 细胞释放核因子-κB 受体活化因子配体(receptor activator of nuclear factor-κβ ligand,RANKL)、促单核细胞 RANK 激活,促进破骨细胞形成,破骨细胞吸收动脉硬化斑块钙化,导致斑块不稳定,增加斑块破裂和血栓形成危险。FSH 还可通过血管内皮细胞 FSHR 诱导血管生成,促进血管细胞黏附分子(vascular cell adhesion molecule,VCAM)1 合成增加,募集单核细胞,影响单核细胞迁移,提高单核细胞与内皮细胞的黏附,促进巨噬细胞分化,形成泡沫细胞。另外,FSH 增加巨噬细胞合成炎性因子 IL-6 与 TNFα,促发低度炎性状态、动脉硬化形成及胰岛素抵抗[3,5]。

基础研究证明,FSH 可通过脂肪细胞、单核细胞 FSHR 刺激增加脂肪合成。FSH 与 FSHR 结合通过偶连抑制型 G 蛋白 α(Gαi)直接刺激脂肪细胞和小鼠成纤维细胞,上调脂肪基因 *Fas*、*Lpl*、*Pparg* 表达,诱导脂肪合成;激活 FSHR 还可降低 cAMP,失活转基因鼠棕色脂肪细胞解偶联蛋白 1(uncoupling protein 1,UCP1)。肥胖的特征为白色脂肪(white adipose tissue,WAT)过多,UCP1 可将 WAT 转化为褐色脂肪。敲除 FSHR 可减弱 FSH 的促进脂肪合成和储存作用。小鼠阻断 FSH 可上调褐色脂肪细胞 *Cox*7、*Cox*8*a*、*Ucp*1、*Cidea* 基因,促进脂肪细胞"米色"转变[3]。

临床研究观察到,FSH 浓度≥7 IU/L 的绝经前妇女血清总胆固醇水平显著高于 FSH<7 IU/L 者;更年期女性 FSH 浓度显著升高,动脉硬化斑块数量增加,绝经后女性 FSH 水平变化与血管炎症关系密切,随 FSH 升高 IMT 增加,心脑血管病风险显著增高,而低 FSH 女性,颈动脉硬化轻,IMT 低[5,21,22]。横断面人群研究显示,与糖尿病无冠心病人群比较,男性糖尿病伴冠心病患者血浆 FSH、LH 浓度显著升高,绝经后女性患者无明显差异,与糖尿病慢性肾病患者比较,糖尿病慢性肾病伴冠心病男性、绝经后女性患者 FSH 与 LH 浓度均明显升高[23]。Osadnik 等[24]报道,有早发冠心病家族史的年轻男性(年龄≥18~35 岁),LH 每升高 1 mIU/ml,早发冠心病危险增加 1.16 倍(OR=1.02~1.32,P=0.03)。新近大样本数据显示,中年男性 LH 浓度与高血压分级、2 级高血压患者发生脑卒中及冠心病的风险呈正相关[18]。老年人高 LH 与衰弱[25]、老年男性糖尿病、ASCVD 及肿瘤风险增加有关[26]。

然而,临床研究结果不尽相同,McCarthy 等[27]观察到(男性占 72.0%),血管阻塞的外周血管病(peripheral arterial disease,PAD)患者血 FSH 浓度低于无血管阻塞 PAD。Chosich 等[28]发现,18~40 岁男、女性正常成人快速输入胰岛素、脂血,形成高胰岛素、高脂血症可显著降低 LH、FSH 水平;男性利拉鲁肽治疗后 FSH 和 LH 水平显著升高,但体质量减轻[29]。

亚洲、欧、美研究结果相近,女性绝经后 FSH 升高可发挥有益的心血管保护作用,FSH 水平与收缩压、血脂异常、糖尿病前期/糖尿病危险、ASCVD 危险因素升高呈负相关[30-32],绝经后女性 FSH 浓度与 IMT 呈负相关[33],前瞻性研究基线/随访血糖正常、基线血糖正常→空腹血糖受损、基线/随访均为空腹血糖受损和基线空腹血糖受损→糖尿病等 4 组观察对象 5 年,结果表明,从 1 组到 4 组 FSH、LH 浓度逐步降低(P<0.001)。logistic 回归分析显示,标准化 FSH 浓度每下降 1 标准差则空腹血糖受损危险增加 3 倍、胰岛素抵抗(稳态模型评估,胰岛素抵抗指数>2.0)和糖尿病危险增加 5 倍,LH 浓度降低者糖尿病危险性增加 2 倍。LH/FSH 比值降低与空腹血糖受损关系密切[34]。

与女性不同,不同年龄男性FSH和LH水平变化与体质量指数增高、肥胖、糖尿病及代谢综合征无明显相关[3,35]。临床研究分别比对中年男性冠心病患者伴或无糖尿病[36],高血压/血糖正常、合并糖尿病前期、合并2型糖尿病中年男性患者(50~65岁)[37]血清LH、FSH浓度,结果均无显著差异。上述研究结果不同的确切原因未明。

5 结 语

垂体促性腺激素除对生殖系统功能有重要影响外,参与多种重要的机体老化相关疾病的发展,特别是ASCVD、脂肪和骨代谢异常。随着年龄增加,中枢神经功能减退,FSH和LH合成、分泌发生变化,可能是这些疾病防治的重要环节和靶点。促性腺激素变化与ASCVD关系复杂,存在心血管、代谢保护或促进异常发生双重作用及性别差异。对此目前尚无明确的认识,可能与促性腺激素合成、释放受下丘脑、卵巢、垂体细胞自分泌/旁分泌复杂调节因素影响有关[1,2,7],因此阐明中枢神经系统功能变化与老化相关疾病的关系具有重要意义。

【参考文献】

[1] Padmanabhan V, Cardoso RC. Neuroendocrine, autocrine, and paracrine control of follicle-stimulating hormone secretion[J]. Mol Cell Endocrinol, 2020, 500: 110632. DOI: 10.1016/j.mce.2019.110632.

[2] Das N, Kumar TR. Molecular regulation of follicle-stimulating hormone synthesis, secretion and action[J]. J Mol Endocrinol, 2018, 60(3): R131-R155. DOI: 10.1530/JME-17-0308.

[3] Lizneva D, Rahimova A, Kim SM, *et al*. Fsh beyond fertility[J]. Front Endocrinol (Lausanne), 2019, 10: 136. DOI: 10.3389/fendo.2019.00136.

[4] Zaidi M, Lizneva D, Kim SM, *et al*. Fsh, bone mass, body fat, and biological aging[J]. Endocrinology, 2018,159(10): 3503-3514. DOI: 10.1210/en.2018-00601.

[5] Sohrabji F, Okoreeh A, Panta A. Sex hormones and stroke: beyond estrogens[J]. Horm Behav, 2019, 111:87-95. DOI: 10.1016/j.yhbeh.2018.10.010.

[6] Stamatiades GA, Carroll RS, Kaiser UB. Gnrh-a key regulator of FSH[J]. Endocrinology, 2019, 160(1): 57-67. DOI: 10.1210/en.2018-00889.

[7] Stamatiades GA, Kaiser UB. Gonadotropin regulation by pulsatile GnRH: signaling and gene expression[J]. Mol Cell Endocrinol, 2018, 463:131-141. DOI: 10.1016/j.mce.2017.10.015.

[8] Kim GW, Park K, Jeong GW. Effects of sex hormones and age on brain volume in post-menopausal women[J]. J Sex Med, 2018, 15(5): 662-670. DOI: 10.1016/j.jsxm.2018.03.006.

[9] Ettinger AM, Gust SK, Kutzler MA. Luteinizing hormone receptor expression by nonneoplastic and neoplastic canine lymphocytes[J]. Am J Vet Res, 2019, 80(6): 572-577. DOI: 10.2460/ajvr.80.6.572.

[10] Burow S, Mizrahi N, Maugars G, *et al*. Characterization of gonadotropin receptors FSHR and LHR in Japanese medaka, Oryzias latipes[J]. Gen Comp Endocrinol, 2020, 285: 113276. DOI: 10.1016/j.ygcen.2019.113276.

[11] Chen H, Cui Y, Yu S. Expression and localisation of FSHR, GHR and LHR in different tissues and reproductive organs of female yaks[J]. Folia Morphol (Warsz), 2018, 77(2): 301-309. DOI: 10.5603/FM.a2016.0095.

[12] Wu XY, Wu XP, Xie H, *et al*. Age-related changes in biochemical markers of bone turnover and gonadotropin levels and their relationship among Chinese adult women[J]. Osteoporos Int, 2010, 21(2): 275-285. DOI: 10.1007/s00198-009-0943-9.

[13] Xia F, Wang N, Han B, *et al*. Hypothalamic-pituitary-gonadal axis in aging men and women: increasing total testosterone in aging men[J]. Neuroendocrinology, 2017, 104(3): 291-301. DOI: 10.1159/000446656.

[14] Meeran D, Urbanski HF, Gregory SJ, *et al*. Developmental changes in the hormonal identity of gonadotroph cells in the rhesus monkey pituitary gland[J]. J Clin Endocrinol Metab, 2003, 88(6): 2934-2942. DOI: 10.1210/jc.2002-021001.

[15] Čukuranović Kokoris J, Jovanovic I, Pantovic V, *et al*. Morphometric analysis of the folliculostellate cells and luteinizing hormone gonadotropic cells of the anterior pituitary of the men during the aging process[J]. Tissue Cell, 2017, 49(1): 78-85. DOI: 10.1016/j.tice.2016.11.006.

[16] Fletcher PA, Smiljanic K, Maso Previde R, *et al*. Cell type- and sex-dependent transcriptome profiles of rat anterior pituitary cells[J]. Front Endocrinol (Lausanne), 2019,10: 623. DOI: 10.3389/fendo.2019.00623.

[17] Cannarella R, Barbagallo F, Condorelli RA, *et al*. Osteoporosis from an endocrine perspective: the role of hormonal changes in the elderly[J]. J Clin Med, 2019, 8(10): 1564. DOI: 10.3390/jcm8101564.

[18] Qu M, Feng C, Wang X, *et al*. Association of serum testosterone and luteinizing hormone with blood pressure and risk of cardiovascular disease in middle-aged and elderly men[J]. J Am Heart Assoc, 2021,10: e019559. DOI: 10.1161/JAHA.120.019559.

[19] Crawford ED, Schally AV. The role of FSH and LH in prostate cancer and cardiometabolic comorbidities[J]. Can J Urol, 2020, 27(2): 10167-10173.

[20] Jabbour R, Ott J, Eppel W, *et al*. Carotid intima-media thickness in polycystic ovary syndrome and its association with hormone and

lipid profiles[J]. PLoS One, 2020, 15(4): e0232299. DOI: 10.1371/journal.pone.0232299.

[21] Sanchez-Barajas M, Ibarra-Reynoso LDR, Ayala-Garcia MA, *et al*. Flow mediated vasodilation compared with carotid intima media thickness in the evaluation of early cardiovascular damage in menopausal women and the influence of biological and psychosocial factors[J]. BMC Womens Health, 2018, 18(1): 153. DOI: 10.1186/s12905-018-0648-3.

[22] El Khoudary SR, Thurston RC. Cardiovascular implications of the menopause transition: endogenous sex hormones and vasomotor symptoms[J]. Obstet Gynecol Clin North Am, 2018, 45(4): 641-661. DOI: 10.1016/j.ogc.2018.07.006.

[23] Wang C, Zhang W, Wang Y, *et al*. Novel associations between sex hormones and diabetic vascular complications in men and postmenopausal women: a cross-sectional study[J]. Cardiovasc Diabetol, 2019, 18(1): 97. DOI: 10.1186/s12933-019-0901-6.

[24] Osadnik T, Pawlas N, Osadnik K, *et al*. High progesterone levels are associated with family history of premature coronary artery disease in young healthy adult men[J]. PLoS One, 2019, 14(4): e0215302. DOI: 10.1371/journal.pone.0215302.

[25] Swiecicka A, Eendebak R, Lunt M, *et al*. Reproductive hormone levels predict changes in frailty status in community-dwelling older men: European male ageing study prospective data[J]. J Clin Endocrinol Metab, 2018, 103(2): 701-709. DOI: 10.1210/jc.2017-01172.

[26] Eendebak R, Ahern T, Swiecicka A, *et al*. Elevated luteinizing hormone despite normal testosterone levels in older men-natural history, risk factors and clinical features[J]. Clin Endocrinol (Oxf), 2018, 88(3): 479-490. DOI: 10.1111/cen.13524.

[27] McCarthy CP, Ibrahim NE, van Kimmenade RRJ, *et al*. A clinical and proteomics approach to predict the presence of obstructive peripheral arterial disease: from the catheter sampled blood archive in cardiovascular diseases (CASABLANCA) study[J]. Clin Cardiol, 2018, 41(7): 903-909. DOI: 10.1002/clc.22939.

[28] Chosich J, Bradford AP, Allshouse AA, *et al*. Acute recapitulation of the hyperinsulinemia and hyperlipidemia characteristic of metabolic syndrome suppresses gonadotropins[J]. Obesity (Silver Spring), 2017, 25(3): 553-560. DOI: 10.1002/oby.21754.

[29] Jensterle M, Podbregar A, Goricar K, *et al*. Effects of liraglutide on obesity-associated functional hypogonadism in men[J]. Endocr Connect, 2019, 8(3): 195-202. DOI: 10.1530/EC-18-0514.

[30] Jung ES, Choi EK, Park BH, *et al*. Serum follicle-stimulating hormone levels are associated with cardiometabolic risk factors in post-menopausal korean women[J]. J Clin Med, 2020, 9(4): 1161. DOI: 10.3390/jcm9041161.

[31] Cheung CL, Kung AWC, Tan KCB. Serum follicle stimulating hormone is associated with reduced risk of diabetes in postmenopausal women: the Hong Kong osteoporosis study[J]. Maturitas, 2018, 114: 41-45. DOI: 10.1016/j.maturitas.2018.05.011.

[32] Wang N, Shao H, Chen Y, *et al*. Follicle-stimulating hormone, its association with cardiometabolic risk factors, and 10-year risk of cardiovascular disease in postmenopausal women[J]. J Am Heart Assoc, 2017, 6(9): e005918. DOI: 10.1161/JAHA.117.005918.

[33] Bertone-Johnson ER, Virtanen JK, Nurmi T, *et al*. Follicle-stimulating hormone levels and subclinical atherosclerosis in older postmenopausal women[J]. Am J Epidemiol, 2018, 187(1): 16-26. DOI: 10.1093/aje/kwx174.

[34] Stefanska A, Cembrowska P, Kubacka J, *et al*. Gonadotropins and their association with the risk of prediabetes and type 2 diabetes in middle-aged postmenopausal women[J]. Dis Markers, 2019, 2019: 2384069. DOI: 10.1155/2019/2384069.

[35] Yamacake KG, Cocuzza M, Torricelli FC, *et al*. Impact of body mass index, age and varicocele on reproductive hormone profile from elderly men[J]. Int Braz J Urol, 2016, 42(2): 365-372. DOI: 10.1590/S1677-5538.IBJU.2014.0594.

[36] Raza MT, Sharif S, Khan ZA, *et al*. Frequency of hypogonadism in type 2 diabetes mellitus patients with and without coronary artery disease[J]. Cureus, 2019, 11(12): e6500. DOI: 10.7759/cureus.6500.

[37] Schianca GP, Fra GP, Brustia F, *et al*. Testosterone plasma concentration is associated with insulin resistance in male hypertensive patients[J]. Exp Clin Endocrinol Diabetes, 2017, 125(3): 171-175. DOI: 10.1055/s-0042-121492.

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