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妊娠期糖尿病孕妇胎盘中 HIF-1α、ET-1 及 VEGF 的表达及与妊娠结局的关系研究 *

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摘要 目的:探讨妊娠期糖尿病孕妇胎盘中缺氧诱导因子 -1α(HIF-1α)、内皮素 -1(ET-1)及血管内皮生长因子(VEGF)的表达及与妊娠结局的关系。**方法:**选取 2015 年 8 月至 2016 年 10 月间济南市中心医院收治的妊娠期糖尿病患者 80 例。根据患者血糖控制效果分为血糖控制不良组(A 组)40 例和血糖控制良好组(B 组)40 例,另取同期于我院体检的健康孕妇 40 例为 C 组。应用免疫组化 SP 法检测各组胎盘中 HIF-1α、ET-1 及 VEGF 的表达情况,观察各组不良妊娠结局发生情况,并分析妊娠期糖尿病孕妇胎盘中 HIF-1α、ET-1 及 VEGF 的表达与妊娠结局相关性。**结果:**A 组孕妇胎盘中 HIF-1α、ET-1 及 VEGF 的阳性表达率均高于 B 组与 C 组,B 组 HIF-1α、VEGF 的阳性表达率高于 C 组(P<0.05)。A 组羊水过多、巨大儿、产后出血的发生率均高于 B 组与 C 组,胎儿窘迫、妊娠高血压的发生率高于 C 组,B 组胎儿窘迫、羊水过多、产后出血、妊娠高血压的发生率高于 C 组(P<0.05)。经 Spearman 相关性分析可得,妊娠期糖尿病孕妇胎盘中 HIF-1α、ET-1 及 VEGF 的表达与妊娠高血压、产后出血、巨大儿、羊水过多、胎儿窘迫等不良妊娠结局呈正相关(P<0.05)。**结论:**妊娠期糖尿病孕妇胎盘中 HIF-1α、ET-1 及 VEGF 呈高表达,其表达会增加不良妊娠结局的发生率。

关键词:妊娠期糖尿病;缺氧诱导因子 -1α;内皮素 -1;血管内皮生长因子;妊娠结局;相关性

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The Relationship Research between the Expression of HIF-1α, ET-1, VEGF in Placenta of Pregnant Women with Gestational Diabetes and the Pregnancy Outcome*

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ABSTRACT Objective: To investigate the relationship between the expression of hypoxia inducible factor-1α (HIF-1α), endothelin-1(ET-1), vascular endothelial growth factor (VEGF) in placenta of pregnant women with gestational diabetes and the pregnancy outcome. **Methods:** 80 cases of gestational diabetes treated in Ji'nan Central Hospital from August 2015 to October 2016 were selected. According to the effect of blood glucose control, the patients were divided into poor control of blood glucose of 40 cases (group A) and good control of blood glucose of 40 cases (group B), 40 cases of healthy pregnant women in the same period in our hospital were selected as group C. The expression of HIF-1α, ET-1, VEGF in placenta of each group were detected by immunohistochemical SP method. The incidence of adverse pregnancy outcomes in each group were observed. The correlation between the expression of HIF-1α, ET-1, VEGF in placenta of pregnant women with gestational diabetes and the pregnancy outcome were analyzed. **Results:** The positive expression rate of HIF-1α, ET-1, VEGF in group A were higher than that in group B and group C, the positive expression rate of HIF-1α, VEGF in group B were higher than that in group C (P<0.05). The incidence of hydramnios, macrosomia and postpartum hemorrhage in group A were higher than that in group B and group C, the incidence of fetal distress and hypertension of pregnancy were higher than that in group C, and the incidence of fetal distress, hydramnios, postpartum hemorrhage and hypertension of pregnancy in group B were higher than that in group C (P<0.05). Spearman correlation analysis showed that the expressions of HIF-1α, ET-1, VEGF in placenta of pregnant women

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with gestational diabetes were positively correlated with adverse pregnancy outcomes such as hypertension of pregnancy, post- partum hemorrhage, macrosomia, hydramnios and fetal distress (P<0.05). **Conclusion:** The high expression of HIF-1α, ET-1, VEGF in placenta of pregnant women with gestational diabetes can increase the incidence of bad pregnancy outcomes.

Key words: Gestational diabetes; Hypoxia inducible factor-1α; Endothelin-1; Vascular endothelial growth factor; Pregnancy outcome; Correlation

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前言

妊娠期糖尿病是妊娠期常见疾病,发病率约占全部妊娠的1%-14%,近年来随着社会的发展和饮食结构的改变,我国妊娠期糖尿病发病率呈升高趋势[1-3]。研究表明[4],妊娠期糖尿病不仅会对产妇产生不利影响,还会增加不良妊娠结局的发生率,导致新生儿发生低血糖症、呼吸窘迫综合征等,严重影响了胎儿的生命健康。目前,关于妊娠期糖尿病发病机制仍未完全明确,一般认为其可能与胎盘血管调节紊乱、分泌抗胰岛素物质以及激素调节紊乱等有关[5,6]。缺氧诱导因子-1α(Hypoxia inducible factor-1α,HIF-1α)是机体组织和细胞在缺氧条件下产生的重要调节因子,主要可通过对相应的靶基因进行调控,从而引发一系列的病理生理反应[7,8]。而血管内皮生长因子(Vascular endothelial growth factor,VEGF)与内皮素-1(Endothelin-1,ET-1)均为HIF-1α的下游靶基因,参与血管形成、血管收缩反应等重要病理生理过程[9,10]。近年来研究发现,妊娠期糖尿病患者胰岛素、血糖水平可以调节HIF-1α,并启动一系列反应,这些反应可能影响妊娠结局[11]。本文通过研究妊娠期糖尿病孕妇胎盘中HIF-1α、ET-1及VEGF的表达,目的在于探讨三者变化与妊娠期糖尿病孕妇妊娠结局的关系,为临床进一步研究妊娠期糖尿病提供参考依据。现作如下报道。

1 资料和方法

1.1 一般资料

将2015年8月至2016年10月间济南市中心医院收治的80例妊娠期糖尿病患者纳入此研究。纳入标准:(1)所有孕妇均符合美国糖尿病协会(American Diabetes Association,ADA)制定的妊娠期糖尿病诊断标准[12];(2)患者均签署了知情同意书;(3)单胎妊娠者。排除标准:(1)伴有心、肝、肾等脏器严重功能障碍者;(2)妊娠前存在血糖异常者;(3)存在精神障碍者;(4)合并贫血者。根据患者血糖控制效果不同分为血糖控制不良组(A组)40例和血糖控制良好组(B组)40例。另取同期正常孕妇40例为C组。其中A组年龄22-37岁,平均(26.13±2.25)岁。B组年龄23-39岁,平均(25.87± 2.19)岁。C组年龄21-36岁,平均(25.98± 2.21)岁。三组孕妇年龄比较无统计学差异(P>0.05),提示可进行组间对比。济南市中心医院的伦理委员会已批准此次研究。

1.2 研究方法

在无菌条件下分别取所有孕妇分娩出的30 min内的大小为1 cm× 1 cm的胎盘组织3块,过程中尽量避开组织钙化区域以及坏死区域。采用甲醛固定与石蜡包埋。然后应用免疫组织化学法SP法进行半定量检测HIF-1α、ET-1及VEGF的蛋白表达情况。实验步骤:梯度乙醇溶液水化;应用柠檬酸PBS缓冲液冲洗;高温、高压热抗原修复,加入山羊血清并依次滴加一抗、二抗;过夜后进行DAB显色;自来水冲洗,梯度乙醇溶液脱水;二甲苯封片。其中兔抗人VEGF、ET-1单克隆抗体、兔抗人HIF-1α多克隆抗体均购自北京中杉金桥生物技术有限公司,严格按照试剂盒说明书进行操作。

1.3 结果判定[9]

HIF-1α定位于细胞核,ET-1定位于细胞质,VEGF定位于细胞膜和细胞浆,随机取5个高倍镜视野,出现阳性细胞即判定为阳性。

1.4 统计学方法

采用SPSS21.0软件进行统计分析。HIF-1α、ET-1及VEGF的表达情况等计数资料以[n (%)]表示,实施x^2检验,应用Spearman相关性分析HIF-1α、ET-1及VEGF的表达与妊娠结局的相关性,检验水准设置为α=0.05。

2 结果

2.1 三组孕妇胎盘中HIF-1α、ET-1及VEGF的表达情况比较

三组孕妇胎盘中HIF-1α、ET-1及VEGF的表达情况整体比较差异有统计学意义(P<0.05),A组孕妇胎盘中HIF-1α、ET-1及VEGF的阳性表达率均高于B组与C组,B组HIF-1α、VEGF的阳性表达率高于C组(P<0.05)。见表1。

表1 三组孕妇胎盘中HIF-1α、ET-1及VEGF的表达情况比较[n(%)]

Table 1 Comparison of the expression of HIF-1α, ET-1, VEGF in the three groups of pregnant women placenta[n(%)]

Groups	n	HIF-1α	ET-1	VEGF
Group A	40	37(92.50)*#	29(72.50)*#	40(100.00)*#
Group B	40	28(70.00)*	15(37.50)	33(82.50)*
Group C	40	14(35.00)	9(22.50)	16(40.00)
x^2	-	18.482	17.675	21.319
P	-	0.00	0.00	0.00

Note: Compared with group C, *P<0.05; Compared with group B, #P<0.05.

2.2 三组孕妇不良妊娠结局比较

三组孕妇胎儿窘迫、羊水过多、巨大儿、产后出血、妊娠高血压的发生率整体比较有统计学差异（P<0.05），A 组羊水过多、巨大儿、产后出血的发生率均高于 B 组与 C 组，胎儿窘迫、妊娠高血压的发生率高于 C 组，B 组胎儿窘迫、羊水过多、产后出血、妊娠高血压的发生率高于 C 组（P<0.05）。见表 2。

表 2 三组孕妇不良妊娠结局比较[n(%)]

Table 2 Comparison of undesirable pregnancy outcome in three groups of pregnant women[n(%)]

Pregnancy outcome	Group A(n=40)	Group B(n=40)	Group C(n=40)	x2	P
Premature rupture of membranes	8(20.00)	6(15.00)	2(5.00)	0.156	0.274
Fetal distress	14(35.00)*	8(20.00)*	2(5.00)	5.283	0.000
Hydramnios	25(62.50)*#	7(17.50)*	1(2.50)	10.489	0.000
Macrosomia	26(65.00)*#	7(17.50)	2(5.00)	12.165	0.000
Postpartum hemorrhage	21(52.50)*#	10(25.00)*	3(7.50)	8.226	0.000
Hypertension of pregnancy	17(42.50)*	9(22.50)*	1(2.50)	6.038	0.000

Note: Compared with group C, *P<0.05; Compared with group B, #P<0.05.

2.3 妊娠期糖尿病孕妇胎盘中 HIF-1α、ET-1 及 VEGF 的表达与妊娠结局相关性分析

经 Spearman 相关性分析可得，妊娠期糖尿病孕妇胎盘中 HIF-1α、ET-1 及 VEGF 的表达与妊娠高血压、产后出血、巨大儿、羊水过多、胎儿窘迫等不良妊娠结局呈正相关（P<0.05）。见表 3。

表 3 妊娠期糖尿病孕妇胎盘中 HIF-1α、ET-1 及 VEGF 的表达与妊娠结局相关性分析

Table 3 The correlation analysis of the expression of HIF-1α, ET-1, VEGF and pregnancy outcome in placenta of pregnant women with gestational diabetes mellitus

Pregnancy outcome	HIF-1α		ET-1		VEGF	
	r	P	r	P	r	P
Fetal distress	0.485	0.006	0.512	0.004	0.503	0.001
Hydramnios	0.332	0.000	0.718	0.000	0.345	0.000
Macrosomia	0.412	0.000	0.822	0.000	0.476	0.000
Postpartum hemorrhage	0.587	0.000	0.701	0.000	0.511	0.000
Hypertension of pregnancy	0.569	0.000	0.592	0.000	0.304	0.000

3 讨论

近年来，随着妊娠期糖尿病的发生率日益增加，其对母婴健康造成了严重威胁，是目前临床上所关注的重点[13-15]。孕妇胎盘是胎儿维系母体的重要器官，而妊娠期糖尿病会导致胎盘的细胞功能、基底膜以及细胞外基质出现异常，从而对新生儿的生长发育造成严重影响，甚至会导致新生儿死亡[16,17]。目前对于妊娠期糖尿病的具体发病机制尚未完全明确，但有研究结果表明其与 2 型糖尿病的发病机制具有相似之处[18]。胎盘在妊娠期糖尿病发病中的作用逐渐引起医学者们的重视，研究发现，随着妊娠进展，胎盘发育并分泌大量的抗胰岛素激素，导致血糖调节异常，而产后胎盘排出体外，胎盘分泌抗胰岛素物质消失，产妇血糖恢复正常[19]。在这一过程中，妊娠期糖尿病患者胰岛素、血糖水平可以通过调节 HIF-1α，启动一系列的反应，并影响妊娠结局[20]，但目前关于这一具体作用机制仍不明确。VEGF 是 HIF-1α 重要的下游靶基因，它主要在滋养细胞、血管内皮细胞和绒毛间质细胞中表达，在胎盘血管形成中起到重要作用[21]。ET-1 也是 HIF-1α 重要的下游因子。研究表明 HIF-1α 的表达增加可以作用于血管内皮细胞，导致 ET-1 生成，引起血管收缩反应[22]。因此，HIF-1α、VEGF 、ET-1 可能共同参与妊娠期糖尿病，并影响妊娠结局。

本研究结果发现，A 组孕妇胎盘中 HIF-1α、ET-1 及 VEGF 的阳性表达率均高于 B 组与 C 组，B 组 HIF-1α、VEGF 的阳性表达率高于 C 组（P<0.05），说明了 HIF-1α、ET-1 及 VEGF 可能在妊娠期糖尿病孕妇的胎盘组织病理生理过程中发挥着一定作用。与此同时，A 组羊水过多、巨大儿、产后出血的发生率均高于 B 组与 C 组，胎儿窘迫、妊娠高血压的发生率高于 C 组，B 组胎儿窘迫、羊水过多、产后出血、妊娠高血压的发生率高于 C 组（P<0.05）。这表明了妊娠期糖尿病是临床上不良妊娠结局的危险因素。究其原因，笔者认为在正常的妊娠过程中，于孕 10 周左右胚胎滋养叶细胞便会开始侵入母体脱膜，以增加血流动力，为胚盘以及胚胎的发育提供足够营养[23,24]。而妊娠期糖尿病孕妇存在着一定程度的糖耐量异常，从而会导致其出现胰岛素代谢异常，进一步导致了糖代谢异常，最终使得胚盘以及胚胎的发育无法得到足够营养，增加了不良妊娠结局发生的风险[25,26]。此外，经 Spearman 相关性分析可得，妊娠期糖尿病孕妇胎盘中 HIF-1α、ET-1 及 VEGF 的表达与妊娠高血压、产后出血、巨大儿、羊水过多、胎儿窘迫等不良妊娠结局呈正相关（P<0.

05），说明了妊娠期糖尿病孕妇胎盘中 HIF-1α、ET-1 及 VEGF 的表达可能参与了不良妊娠结局的发生、发展，并在其中起着至关重要的作用。其中 HIF-1α 主要是通过刺激靶基因转录，从而引发细胞对缺氧的适应性反应，有效维持机体的氧稳态。ET-1 则可在缺氧环境下与 HIF-1α 进行特异性结合，从而引起胎盘滋养细胞过度氧化应激，进一步导致胎盘出现局部损伤[27-29]。VEGF 的高表达则会导致胎盘组织细胞出现缺血缺氧以及异常血管增生等病理生理改变，从而使得胎儿处于缺氧状态，进一步增加了不良妊娠结局的发生，这在 Yu Z 等人的研究报道可加以佐证[30]。

综上所述，孕妇胎盘中 HIF-1α、ET-1 及 VEGF 参与了妊娠期糖尿病的病理生理过程，且与不良妊娠结局的发生、发展密切相关，临床中可将 HIF-1α、ET-1 及 VEGF 作为治疗靶点，从而改善患者预后。

参 考 文 献（References）

[1] PLOS ONE Staff. Correction: Circulating Betatrophin Levels and Gestational Diabetes Mellitus:A Systematic Review and Meta-Analysis [J]. PLoS One, 2017, 12(2): 172449-172500

[2] Kumari R, Singh H. The prevalence of elevated high-sensitivity C-reactive protein in normal pregnancy and gestational diabetes mellitus [J]. J Family Med Prim Care, 2017, 6(2): 259-264

[3] Prakash GT, Das AK, Habeebullah S, et al. Maternal and Neonatal Outcome in Mothers with Gestational Diabetes Mellitus [J]. Indian J Endocrinol Metab, 2017, 21(6): 854-858

[4] Ostadrahimi A, Mohammad-Alizadeh S, Mirgafourvand M, et al. Effects of Fish Oil Supplementation on Gestational Diabetes Mellitus (GDM):A Systematic Review [J]. Iran Red Crescent Med J, 2016, 18 (11): 24690-24691

[5] Liao S,Vickers MH,Taylor RS,et al.Maternal serum placental growth hormone, insulin-like growth factors and their binding proteins at 20 weeks' gestation in pregnancies complicated by gestational diabetes mellitus[J]. Hormones (Athens), 2017, 16(3): 282-290

[6] Gjesing AP, Rui G, Lauenborg J, et al. High Prevalence of Diabetes-Predisposing Variants in MODY Genes Among Danish Women With Gestational Diabetes Mellitus [J]. J Endocr Soc, 2017, 1 (6): 681-690

[7] Li H, Shen L, Song L, et al. Early age at menarche and gestational diabetes mellitus risk: Results from the Healthy Baby Cohort study[J]. Diabetes Metab, 2017, 3636(17): 30006-30007

[8] Wang S, Wang X, Weng Z, et al. Expression and role of microRNA 18b and hypoxia inducible factor-1α in placental tissues of preeclampsia patients[J]. Exp Ther Med, 2017, 14(5): 4554-4560

[9] 赵骏达,武建利,李燕,等.二甲双胍联合津力达颗粒治疗妊娠期糖尿病的临床效果及对患者血清 VEGF、APN、Hcy 水平的影响[J].现代生物医学进展, 2017, 17(25): 4869-4872
Zhao Jun-da, Wu Jian-li, Li Yan, et al. Curative Efficacy of Metformin Combined with Jinlida Granules in Treatment of Gestational Diabetes Mellitus and Its Effects on Serum VEGF, APN and Hcy Levels [J]. Progress in Modern Biomedicine, 2017, 17(25): 4869-4872

[10] Zhang J, Yao J, Zhao Y, et al. Association Between Serum Free Fatty Acids Levels and Gestational Diabetes Mellitus: a Cross-Sectional Study[J]. Clin Lab, 2017, 63(1): 15-20

[11] Görkem Ü, Küçükler FK, Toğrul C, et al. Are adipokines associated with gestational diabetes mellitus? [J]. J Turk Ger Gynecol Assoc, 2016, 17(4): 186-190

[12] 宋依临,杨慧霞.妊娠期糖尿病孕妇不同血糖监测方法的评价[J].中华妇产科杂志, 2012, (10): 797-799
Song Yi-lin, Yang Hui-xia. Evaluation of different blood glucose monitoring methods for pregnant women with gestational diabetes[J]. Chinese Journal of Obstetrics and Gynecology, 2012, (10): 797-799

[13] Taousani E, Savvaki D, Tsirou E, et al. Regulation of basal metabolic rate in uncomplicated pregnancy and in gestational diabetes mellitus [J]. Hormones (Athens), 2017, 16(3): 235-250

[14] Chung SM, Moon JS. Simple Screening Using Ultrasonography for Prediction of Gestational Diabetes Mellitus [J]. Diabetes Metab J, 2017, 41(6): 438-439

[15] Jamilian M, Samimi M, Faraneh AE, et al. Magnesium supplementation affects gene expression related to insulin and lipid in patients with gestational diabetes[J]. Magnes Res, 2017, 30(3): 71-79

[16] Zhou J, Ni X, Huang X, et al. Potential Role of Hyperglycemia in Fetoplacental Endothelial Dysfunction in Gestational Diabetes Mellitus [J]. Cell Physiol Biochem, 2016, 39(4): 1317-1328

[17] 屈莉红,荆鲁宁.胎盘组织缺氧诱导因子 -1α 和内皮素 -1 表达对糖尿病妊娠的影响[J].中国现代医学杂志, 2016, 26(20): 44-47
Qu Li-hong, Jing Lu-ning. Influence of placental hypoxia inducible factor-1α and endothelin-1 in gestational diabetes patients [J]. China Journal of Modern Medicine, 2016, 26(20): 44-47

[18] Fuchs S, Gat-Yablonski G, Shtaif B, et al. Vascular endothelial growth factor (VEGF) levels in short, GH treated children: a distinct pattern of VEGF-C in Noonan syndrome [J]. J Endocrinol Invest, 2015, 38(4): 399-406

[19] Long DS, Hou W, Taylor RS, et al. Serum levels of endothelial glycocalyx constituents in women at 20 weeks' gestation who later develop gestational diabetes mellitus compared to matched controls: a pilot study[J]. BMJ Open, 2016, 6(12): 11244-11245

[20] Zhu L, Zhao Q. Hypoxia-inducible factor 1α participates in hypoxia-induced epithelial-mesenchymal transition via response gene to complement 32[J]. Exp Ther Med, 2017, 14(2): 1825-1831

[21] Wei J, Jiang H, Gao H, et al. Blocking Mammalian Target of Rapamycin (mTOR) Attenuates HIF-1α Pathways Engaged-Vascular Endothelial Growth Factor (VEGF) in Diabetic Retinopathy[J]. Cell Physiol Biochem, 2016, 40(6): 1570-1577

[22] Lin Y, Tang Y, Wang F, et al. The Protective Effect of HIF-1α in T Lymphocytes on Cardiac Damage in Diabetic Mice [J]. Ann Clin Lab Sci, 2016, 46(1): 32-43

[23] Troncoso F, Acurio J, Herlitz K, et al. Gestational diabetes mellitus is associated with increased pro-migratory activation of vascular endothelial growth factor receptor 2 and reduced expression of vascular endothelial growth factor receptor 1 [J]. PLoS One, 2017, 12 (8): e0182509

[24] Mizia-Malarz A, Sobol-Milejska G. Assessment of Angiogenesis in Children with Acute Lymphoblastic Leukemia Based on Serum Vascular Endothelial Growth Factor Assay[J]. Indian J Med Paediatr Oncol, 2017, 38(3): 321-325

（下转第 3288 页）

[17] Rasheed Z, Al-Shobaili HA, Rasheed N, et al. Integrated Study of Globally Expressed microRNAs in IL-1β-stimulated Human Osteoarthritis Chondrocytes and Osteoarthritis Relevant Genes: A Microarray and Bioinformatics Analysis [J]. Nucleosides Nucleotides Nucleic Acids, 2016, 35(7): 335-355

[18] Kosloski MP, Goss S, Wang SX, et al. Pharmacokinetics and Tolerability of a Dual Variable Domain Immunoglobulin ABT-981 Against IL-1α and IL-1β in Healthy Subjects and Patients with Osteoarthri- tis of the Knee[J]. J Clin Pharmacol, 2016, 56(12): 1582-1590

[19] Wang F, Wu L, Li L, et al. Monotropein exerts protective effects against IL-1β-induced apoptosis and catabolic responses onosteoarthritis chondrocytes [J]. Int Immunopharmacol, 2014, 23 (2): 575-580

[20] Minatani A, Uchida K, Inoue G, et al. Activation of calcitonin gene-related peptide signaling through the prostaglandin E2-EP1/EP2/EP4 receptor pathway in synovium of knee osteoarthritis patients[J]. J Orthop Surg Res, 2016, 11(1): 117

[21] Ahn H, Woods AJ, Kunik ME, et al. Efficacy of transcranial direct current stimulation over primary motor cortex (anode) and contralateral supraorbital area (cathode) on clinical pain severity and mobility performance in persons with knee osteoarthritis: An experimenter and participant-blinded, randomized, sham-controlled pilot clinical study [J]. Brain Stimul, 2017, 10(5): 902-990

[22] Lent PL, Koenders MI, Blaney Davidson EN, et al. IL37 dampens the IL1β-induced catabolic status of human OA chondrocytes [J]. Rheumatology (Oxford), 2017, 56(3): 351-361

[23] Cai H, Sun HJ, Wang YH, et al. Relationships of common polymorphisms in IL-6, IL-1A, and IL-1B genes with susceptibility to osteoarthritis: a meta-analysis [J]. Clin Rheumatol, 2015, 34 (8): 1443-1453

[24] Favre J, Jolles BM. Gait analysis of patients with knee osteoarthritis highlights a pathological mechanical pathway and provides a basis for therapeutic interventions[J]. EFORT Open Rev, 2017, 1(10): 368-374

[25] Li M, Yuan H, Wang P, et al. Influences of De Qi induced by acupuncture on immediate and accumulated analgesic effects in patients with knee osteoarthritis: study protocol for a randomized controlled trial[J]. Trials, 2017, 18(1): 251

[26] Ahn H, Woods AJ, Kunik ME, et al. Efficacy of transcranial direct current stimulation over primary motor cortex (anode) and contralateral supraorbital area (cathode) on clinical pain severity and mobility performance in persons with knee osteoarthritis: An experimenter- and participant-blinded, randomized, sham-controlled pilot clinical study[J]. Brain Stimul, 2017, 10(5): 902-909

[27] Theologis T, Efstathopoulos N, Nikolaou V, et al. Association between serum and synovial fluid Dickkopf-1 levels with radiographic severity in primaryknee osteoarthritis patients [J]. Clin Rheumatol, 2017, 36(8): 1865-1872

[28] Yao N, Chen N, Xu X, et al. Protective effect of Shenmai injection on knee articular cartilage of osteoarthritic rabbits and IL-1β-stimulated human chondrocytes[J]. Exp Ther Med, 2017, 13(6): 3013-3020

[29] Migliore A, Scirè CA, Carmona L, et al. The challenge of the definition of early symptomatic knee osteoarthritis: a proposal of criteria and red flags from an international initiative promoted by the Italian Society for Rheumatology[J]. Rheumatol Int, 2017, 37(8): 1227-1236

[30] Wang C, Zeng L, Zhang T, et al. Tenuigenin Prevents IL-1β-induced Inflammation in Human Osteoarthritis Chondrocytes by Suppressing PI3K/AKT/NF-κB Signaling Pathway[J]. Inflammation, 2016, 39(2): 807-812

(上接第 3326 页)

[25] Güzel D, Dursun AD, Fçıçcılar H, et al. Effect of intermittent hypoxia on the cardiac HIF-1/VEGF pathway in experimental type 1 diabetes mellitus[J]. Anatol J Cardiol, 2016, 16(2): 76-83

[26] Wang Y, Zhang Y, Zhu CG, et al. Big endothelin-1 level is a useful marker for predicting the presence of isolated coronary artery ectasia [J]. Biomarkers, 2017, 22(3-4): 331-336

[27] Shin AN, Dasgupta C, Zhang G, et al. Proteomic Analysis of Endothelin-1 Targets in the Regulation of Cardiomyocyte Proliferation [J]. Curr Top Med Chem, 2017, 17(15): 1788-1802

[28] 梁春娇,黄鑫,王杨,等.血浆 FA、ET-1、Hcy、VEGF 水平与妊娠高血压综合征的相关性研究 [J]. 现代生物医学进展, 2017, 17(27): 5290-5293

Liang Chun-jiao, Huang Xin, Wang Yang, et al. Relationship between Plasma FA, ET-1, Hcy and VEGF Levels and Pregnancy Induced Hypertension [J]. Progress in Modern Biomedicine, 2017, 17 (27): 5290-5293

[29] Zeng Z, Huang WD, Gao Q, et al. Arnebin-1 promotes angiogenesis by inducing eNOS,VEGF and HIF-1α expression through the PI3K-dependent pathway[J]. Int J Mol Med, 2015, 36(3): 685-697

[30] Yu Z, Tang L, Chen L, et al. Role for HIF-1α and Downstream Pathways in Regulating Neuronal Injury after Intracerebral Hemorrhage in Diabetes[J]. Cell Physiol Biochem, 2015, 37(1): 67-76