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脂联素在早产儿血清中的表达及其与体格指标、载脂蛋白和骨密度的关系*

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摘要 目的:探讨脂联素在早产儿血清中的表达水平及其与体格指标、载脂蛋白和骨密度的相关性。**方法:**选择 2017 年 1 月至 2018 年 5 月期间我院新生儿科住院的早产儿 72 例作为研究组,另外选择同期我院出生的足月新生儿 58 例作为对照组。对比两组新生儿的一般资料、脂联素、载脂蛋白和骨密度水平,分析早产儿血清脂联素水平与体格指标、载脂蛋白和骨密度的相关性,同时分析影响血清脂联素水平的危险因素。**结果:**两组受试新生儿的性别、胸围、低密度脂蛋白(LDL-C)及高密度脂蛋白(HDL-C)之间的差异无统计学意义($P>0.05$);研究组新生儿的胎龄、体质量指数(BMI)、身长、头围、总胆固醇(TC)及三酰甘油(TG)明显低于对照组($P<0.05$);与对照组相比,研究组新生儿血清脂联素、载脂蛋白 A-I(Apo A-I)及左胫骨中段超声波在骨骼中的传播速度(SOS)水平明显下降,而载脂蛋白 B(Apo B)和 Apo B/Apo A-I 水平均显著升高,且差异均具有统计学意义($P<0.05$);早产儿血清脂联素水平与胎龄、BMI、头围、TC、TG、Apo A-I 及 SOS 呈正相关($P<0.05$),与 Apo B 和 Apo B/Apo A-I 水平呈负相关($P<0.05$);Logistic 回归结果显示,胎龄、BMI、Apo B/Apo A-I 及 SOS 是早产儿血清脂联素水平的影响因素($P<0.05$)。**结论:**早产儿血清脂联素水平低于足月儿,血清脂联素水平与体格指标、载脂蛋白及骨密度密切相关,可能对新生儿的生长发育具有重要的调节作用。

关键词:脂联素;早产儿;体格指标;载脂蛋白;骨密度;相关性

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Expression of Serum Adiponectin in Premature Infants and Its Relationship with Body Mass Index, Apolipoprotein and Bone Mineral Density*

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ABSTRACT Objective: To explore the expression of serum adiponectin in premature infants and its correlation with body mass index, apolipoprotein and bone mineral density. **Methods:** A total of 72 premature infants, who were hospitalized in First Hospital of Hebei Medical University from January 2017 to May 2018 were chosen as research group. In addition, 58 neonatal infants born in this hospital during the same period were chosen as control group. The general data, adiponectin, apolipoprotein and bone mineral density of two groups of neonates were compared, the correlation between serum adiponectin level, body mass index, apolipoprotein and bone mineral density in the preterm infants were analyzed. Meanwhile, the risk factors of serum adiponectin level were analyzed. **Results:** There were no statistically significant differences in the gender, chest circumference, low-density lipoprotein (LDL-C) and high-density lipoprotein (HDL-C) between the two groups($P>0.05$). The gestational age, body mass index (BMI), body length, head circumference, total cholesterol (TC) and three acylglycerol(TG) in the research group were significantly lower than those in the control group ($P<0.05$). Compared with the control group, the serum adiponectin, apolipoprotein A-I (Apo A-I) and the middle segment of the left tibia in the research group decreased significantly in the bone transmission speed (SOS), while the apolipoprotein B (Apo B) and Apo B/Apo A-I levels increased significantly, and the differences were statistically significant ($P<0.05$). The serum adiponectin level in premature infants was positively correlated with gestational age, BMI, head circumference, TC, TG, Apo A-I and SOS($P<0.05$), and which was negatively correlated with Apo B and Apo B/Apo A-I ($P<0.05$). Logistic regression results showed that gestational age, BMI, Apo B/Apo A-I and SOS were the influencing factors of serum adiponectin level in the premature infants ($P<0.05$). **Conclusion:** The level of serum adiponectin of preterm infant is lower than mature infants, and serum adiponectin level is closely related to the body mass index, apolipoprotein and bone mineral density, which may play an important role in the regulation of newborn growth and development.

Key words: Adiponectin; Premature infants; Body mass index; Apolipoprotein; Bone mineral density; Relationship

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前言

新生儿的生长受到多种因素的影响,包括营养、遗传、内分泌及环境等^[1,2]。早产(新生儿胎龄小于 37 周)是一种常见现象,不仅影响新生儿出生后的发育,而且可能引起成人期心血管疾病及糖尿病的发生,严重影响新生儿的生长和代谢^[3-5]。脂肪组织在传统意义上是能量储存器官,近年来研究发现,脂肪组织作为内分泌器官,分泌多种激素进入血液系统,这些激素被称为脂肪细胞因子,参与脂肪代谢及能量合成等生理过程^[6,7]。脂联素是由脂肪组织分泌的脂肪细胞因子,是一种血浆蛋白,能够调节能量代谢和调控新生儿生长发育,同时可以降低血糖及三酰甘油(triacylglycerol, TG)水平,改善心血管内皮功能,抑制动脉粥样硬化形成^[8-10]。另外,早产儿往往骨密度偏低,不利于骨骼的发育,易导致代谢性骨病的发生,而脂联素与相应受体结合后能够直接参与骨代谢过程,但是具体的相关机制有待进一步分析^[11,12]。本研究通过探讨脂联素在早产儿血清中的表达水平及其与体格指标、载脂蛋白和骨密度的相关性,并探讨影响脂联素的因素。

1 资料与方法

1.1 一般资料

选择 2017 年 1 月至 2018 年 5 月期间在我院新生儿科住院的早产儿 72 例作为研究组,纳入标准:① 出生时间为 1 周内;② 胎龄 <37 周;③ 孕妇健康,无任何妊娠期疾病;④ 早产儿的临床资料完整;⑤ 经早产儿家长同意,并签署知情同意书。排除标准:① 合并患有神经系统疾病;② 入组前一周合并严重感染;③ 染色体异常或先天畸形新生儿;④ 接受过糖皮质激素治疗。另外选择同期在我院出生的健康足月新生儿 58 例,作为对照组。所有研究过程均符合我院医学伦理委员会的相关规定。

1.2 方法

1.2.1 临床资料收集 收集受试新生儿的各项基本资料,包括

性别、年龄、体质量指数(Body mass index, BMI)、体格指标(身长、头围、胸围)、血脂水平[总胆固醇(Total cholesterol, TC)、TG、低密度脂蛋白(Low density lipoprotein cholesterol, LDL-C)及高密度脂蛋白(High density lipoprotein cholesterol, HDL-C)]。

1.2.2 血清脂联素检测 抽取受试新生儿外周静脉血 5 mL,置于未涂有肝素钠的采血管中,在室温下静置 20 min,以 3000 r/min 的速度、3 cm 离心半径离心 10 min,分离血清,采用酶联免疫吸附测定法检测血清中脂联素水平,试剂盒购自南京建成生物工程研究所。

1.2.3 生化指标测定 采用免疫透射比浊法测定血清载脂蛋白 A-I(apolipoprotein A-I, Apo A-I)、载脂蛋白 B(apolipoprotein B, Apo B)水平,并计算 Apo B/Apo A-I。试剂盒购自南京建成生物工程研究所。应用日立 7180 型全自动生化分析仪检测血脂水平。

1.2.4 骨密度评估 采用以色列 Sunlight 公司生产的 Omnisense 定量超声仪,根据左胫骨中段超声波在骨骼中的传播速度(Speed of sound, SOS)评估骨密度。

1.3 统计学方法

所有研究数据均在 SPSS21.0 软件上运行处理。受试新生儿血清脂联素、体格指标、载脂蛋白和骨密度水平等计量资料以均数±标准差表示,实施 t 检验;计数资料用百分数(%)表示,实施 χ^2 检验。采用 Pearson 相关性分析方法分析早产儿血清脂联素水平与体格指标、载脂蛋白和骨密度的相关性。对脂联素的影响因素进行 Logistic 回归分析。检验标准设置为 $\alpha=0.05$ 。

2 结果

2.1 比较两组受试新生儿的一般资料

两组受试新生儿的性别、胸围、LDL-C 及 HDL-C 之间的差异无统计学意义($P>0.05$)。研究组新生儿的胎龄、BMI、身长、头围、TC 及 TG 明显低于对照组,且差异均具有统计学意义($P<0.05$),如表 1 所示。

表 1 比较两组受试新生儿的一般资料

Table 1 Comparison of general information of two groups of newborns

Indexes	Control group(n=58)	Research group(n=72)	t/ χ^2	P
Gender(Male/Female)	37/21	43/29	0.225	0.635
Gestational age(weeks)	38.56± 1.91	34.08± 2.02	-12.877	0.000
BMI(kg/m ²)	12.83± 1.73	9.67± 1.65	-10.622	0.000
Length(cm)	50.04± 2.05	46.19± 1.89	-11.117	0.000
Head circumference(cm)	33.87± 1.03	31.13± 0.91	-16.088	0.000
Bust(cm)	32.73± 1.12	32.41± 0.87	-1.834	0.069
TC(mmol/L)	2.98± 1.03	1.21± 0.64	-11.994	0.000
TG(mmol/L)	0.78± 0.31	0.42± 0.22	-7.732	0.000
LDL-C(mmol/L)	2.41± 0.51	2.42± 0.54	0.108	0.914
HDL-C(mmol/L)	1.92± 0.47	1.87± 0.38	-0.671	0.504

2.2 对比两组新生儿血清脂联素、载脂蛋白和骨密度水平

与对照组相比,研究组新生儿血清脂联素、Apo A-I 及 SOS 水平明显降低,而 Apo B 和 Apo B/Apo A-I 水平均明显升高,且差异均具有统计学意义($P<0.05$),如表 2 所示。

2.3 分析早产儿血清脂联素水平与体格指标、载脂蛋白和骨密

度的相关性

早产儿血清脂联素水平与胎龄、BMI、身长、头围、TC、TG、Apo A-I 及 SOS 呈正相关($P<0.05$),与 Apo B 和 Apo B/Apo A-I 水平呈负相关($P<0.05$),而与性别、胸围、LDL-C 及 HDL-C 无相关性($P>0.05$),如表 3 所示。

表 2 对比两组新生儿血清脂联素、载脂蛋白和骨密度水平($\bar{x} \pm s$)Table 2 Comparison of serum adiponectin, apolipoprotein and bone mineral density between two groups of newborns($\bar{x} \pm s$)

Groups	n	Adiponectin(mg/L)	Apo A-I(g/L)	Apo B(g/L)	Apo B/Apo A-I	SOS(m/s)
Control group	58	26.13± 3.06	1.12± 0.21	0.31± 0.08	0.28± 0.07	2887.02± 235.41
Research group	72	17.25± 2.85	0.92± 0.18	0.42± 0.09	0.46± 0.06	2709.18± 202.53
t		-17.088	-5.845	7.276	15.782	-4.628
P		0.000	0.000	0.000	0.000	0.000

表 3 分析早产儿血清脂联素水平与体格指标、载脂蛋白和骨密度的相关性

Table 3 Correlation between serum adiponectin levels and body mass index, apolipoprotein and bone mineral density in preterm infants

Indexes	Serum adiponectin	
	r	P
Gender	0.152	0.513
Gestational age	0.602	0.035
BMI	0.609	0.032
Length	0.618	0.029
Head circumference	0.587	0.041
Bust	0.219	0.403
TC	0.616	0.030
TG	0.637	0.023
LDL-C	0.203	0.600
HDL-C	0.254	0.350
Apo A-I	0.621	0.028
Apo B	-0.592	0.039
Apo B/Apo A-I	-0.606	0.034
SOS	0.643	0.022

2.4 早产儿血清脂联素影响因素的多元回归分析

以脂联素水平变化作为应变量,建立非条件 Logistic 回归模型。由于该应变量是连续变量,故进行分类变量转化:汇总研究组和对照组资料,发现 21 mg/L 是两组脂联素水平的明显分界,研究组(早产组)95%样本均在其上,而对照组 96%均在其下,故以此值进行两分类资料转化,赋值 1=脂联素水平>21 mg/L,0=脂联素水平≤21 mg/L。

自变量为前述表 1 表 2 中 P<0.10 的各种指标,并参考统

计人员建议,去除和 BMI 有一定共线作用的胸围、头围等指标,其它指标则参考其总均值进行两分类转化后纳入分析(赋值参见表 4)。回归过程采用后退法,自变量剔除的 α 退出=0.05。回归结果:胎龄、BMI、Apo B/Apo A-I、SOS 等 4 因素被最终保留于回归模型中($P<0.05$),提示其为早产儿血清脂联素水平变化的影响因素,OR 值在 2~4 区间。其中最高为 Apo B/Apo A-I OR 值为 4.261,是早产儿血清脂联素水平的最大影响因素。详见表 4。

表 4 早产儿血清脂联素影响因素的多元回归分析

Table 4 Multiple regression analysis of influencing factors of serum adiponectin in premature infants

Indexes	Assignment explanation	Regression coefficient	β	Wald χ^2	P	OR	OR 95%
Gestational age	1=premature delivery, 0=normal	0.705	0.312	5.095	0.024	2.024	1.097~3.733
BMI	1=>10 kg/m ² , 0=no	1.143	0.487	5.501	0.019	3.135	1.207~8.145
Apo B/Apo A-I	1=>0.4, 0=no	1.217	0.451	7.273	0.007	3.376	1.394~8.174
SOS	1=>2750 m/s, 0=no	1.450	0.584	6.169	0.013	4.261	1.358~13.375

Note: The boundaries of each index except gestational age in the table are the integral approximation of the total average level of the corresponding two groups.

3 讨论

近年来,脂肪组织作的分泌功能越来越受到人们的关注。除了能够分泌脂联素以外,脂肪组织分泌的激素主要包括促酰

化蛋白、抵抗素、瘦素及胰岛素样生长因子-1 等,其可通过自分泌、内分泌及旁分泌的方式参与调节机体能量代谢及胰岛素抵抗等病理过程^[13-15]。脂肪细胞分泌的脂源性激素影响骨骼的发育,而新生儿的骨骼状况对其生长发育具有重要作用,是成

人期骨骼发育的基础。早产儿的骨矿化程度持续落后,而营养状况对骨骼的生长发育有着重要影响,因此对早产儿骨骼营养状况进行及时准确的评估意义重大^[16,17]。近来研究发现^[18],骨定量超声技术可以评估早产儿骨骼状态,不仅可以测量骨矿物质密度及骨皮质参数,而且能够显示骨骼微结构,研究中选用骨定量超声技术测量受试新生儿的左胫骨 SOS 用于评估骨密度。

脂联素是由脂肪细胞合成并分泌的一种蛋白质,由 244 个氨基酸组成,相对分子量为 28 kD,是可溶性防御性胶原家族成员之一^[19]。脂联素作为一种肥胖因子,影响胎儿的脂肪代谢,随着胎龄的增长,脂肪组织合成的脂联素浓度升高,并释放入血,从而影响胎儿在子宫内的生长发育^[20,21]。脂联素的基因定位于 3q27,包括 3 个外显子和 2 个内含子,其受体分布于全身组织,脂联素将近占人体血浆蛋白的 0.01%,是常见激素的 3 倍,并且不受饮食的变化而改变,无昼夜节律变化,与细胞膜上的受体结合而发挥作用^[22]。脂联素可以提高胰岛素敏感性、抗动脉粥样硬化及改善代谢综合征,同时脂联素具有调节能量代谢、加速脂质氧化及骨代谢的作用,对胎儿的生长发育具有重要意义^[23]。一般资料的对比研究中,研究组新生儿的胎龄、BMI、身长、头围、TC 及 TG 明显低于对照组 ($P < 0.05$),提示这些因素可能影响胎儿的生长发育。同时比较两组新生儿血清相关指标检测,结果发现,与对照组相比,研究组新生儿血清脂联素、Apo A-I 及 SOS 水平明显下降,而 Apo B 和 Apo B/Apo A-I 水平均显著升高 ($P < 0.05$),提示脂联素水平能够用于衡量胎儿体内脂肪储备及新生儿营养状态。新生儿缺乏大体积脂肪细胞,体脂百分比低,与成人的脂肪分布位置不同,从而缺少脂联素生成的负反馈调节机制。另外,胎儿后期是骨矿物质储备的重要时期,早产儿胎龄较短,从母体中获得的骨矿物质少,加上出生后体内的储备量少导致其 SOS 水平明显下降^[24]。进一步的相关性分析结果显示,早产儿血清脂联素水平与胎龄、BMI、身长、头围、TC、TG、Apo A-I 及 SOS 呈正相关 ($P < 0.05$),与 Apo B 和 Apo B/Apo A-I 水平呈负相关 ($P < 0.05$),胎龄、BMI、Apo B/Apo A-I、SOS 是早产儿血清脂联素水平的影响因素 ($P < 0.05$)。胎龄影响脂联素水平,随着胎龄增加,脂肪组织合成更多的脂联素^[25,26]。由于早产儿体重较轻,体内的脂肪含量低从而影响脂联素的合成及分泌量,同时脂肪组织参与机体的能量代谢过程及能量代谢紊乱的相关疾病的发生及发展,最终影响脂联素在血液循环中的量^[27,28]。脂联素影响骨代谢水平已经得到验证,脂联素通过三种代谢途径影响成骨细胞和破骨细胞的活性而参与骨代谢途径,脂联素直接作用于成骨细胞,诱使其增殖和分化,同时通过 MAPK 途径上调核因子 κB 受体活化因子配体表达,阻滞护骨素的表达过程,从而诱导破骨细胞分化,另外,脂联素不仅抑制破骨细胞的活性,而且能够通过促进胰岛素信号转导而激活成骨细胞,增加骨矿水平,提高骨量^[29,30]。早产儿的骨骼发育异常,骨密度下降,破骨细胞与成骨细胞在功能上相对应,二者协同,在骨骼的发育和形成过程中发挥重要作用,具体的骨密度如何影响脂联素的作用尚未见报道,需要进一步的深入研究。

综上所述,脂联素能够预测新生儿的体格发育趋势,并且通过影响血液中载脂蛋白及骨密度水平而参与新生儿的生长发育,检测脂联素能够辅助评估新生儿的发育状况。

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