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论著

肥胖儿童 non-HDL-C、remnant cholesterol 与亚临床动脉粥样硬化的关系

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摘要 目的:了解 non-HDL-C 和 remnant cholesterol 与肥胖儿童亚临床动脉粥样硬化(AS)的关系。方法:根据甘油三酯(TG)水平将 65 例肥胖儿童(肥胖组)分为 I 组($TG \geq 2.3$ mmol/L)32 例,II 组($TG < 2.3$ mmol/L)33 例,与肥胖组儿童性别年龄相匹配的正常体质量儿童 30 例为 III 组(对照组)。比较 3 组儿童血脂指标,对肥胖组各项血脂指标与血浆致动脉粥样硬化指数(AIP)进行相关性分析,肥胖患儿体质指数、血脂指标与颈动脉内径、内膜-中层厚度(c-IMT)、血流参数进行相关性分析。结果:I 组、II 组的 TG、总胆固醇(TC)、低密度脂蛋白胆固醇(LDL-C)、non-HDL-C、remnant cholesterol、AIP 均较对照组升高,高密度脂蛋白胆固醇(HDL-C)较对照组降低,且 I 组的 remnant cholesterol、AIP 均较 II 组升高。肥胖组儿童 AIP 与 TG、non-HDL-C、remnant cholesterol 呈正相关,与 HDL-C 呈负相关。37 例行颈动脉超声检查的肥胖儿童的 c-IMT 较正常儿童的增厚。结论:non-HDL-C、remnant cholesterol 在肥胖儿童亚临床 AS 中有重要作用,在肥胖儿童血脂异常的治疗中应关注 non-HDL-C、remnant cholesterol 的变化。

关键词 儿童肥胖;亚临床动脉粥样硬化;non-HDL-C;remnant cholesterol;血浆致动脉粥样硬化指数;颈动脉内膜-中层厚度
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Relationship between non-HDL-C, remnant cholesterol and subclinical atherosclerosis of obese children

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Abstract **Objective:** To investigate the value of non-HDL-C and remnant cholesterol in the state of subclinical atherosclerosis for obese children. **Methods:** A total of 65 obese children were enrolled in this trial including 37 obese children who performed carotid ultrasound examination. According to the level of triglyceride (TG), these obese children were divided into two groups: group I ($n=32$, $TG \geq 2.3$ mmol/L) and group II ($n=33$, $TG < 2.3$ mmol/L). Thirty healthy children whose age and sex were matched served as the control group. Serum lipid parameters of the three groups were compared. The relationships between the lipid metabolic indices, non-HDL-C, remnant cholesterol and atherogenic index of plasma (AIP) in the obese group were analyzed. The relationships between all of the indices and the intima-media thickness(c-IMT), inner diameter, peak flow of the carotid artery of the obese children who performed carotid ultrasound examination were also analyzed. **Results:** Triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), non-HDL-C, remnant cholesterol, AIP in the obese group (group I and group II) were significantly higher than that of the control group, but HDL-C of the obese group was lower than that of the control group. The levels of remnant cholesterol and AIP in group I were higher than that in group II. TG, non-HDL-C and remnant cholesterol were correlated with AIP of the obese group. The c-IMT of the obese children who performed carotid ultrasound examination was thicker than that of the normal children. **Conclusion:** Non-HDL-C and remnant cholesterol play an important role in the state of subclinical atherosclerosis for obese children. Non-HDL-C and remnant cholesterol should be taken into account in the lipid-lowering for obese children.

Key words childhood obesity; subclinical atherosclerosis; non-HDL-C; remnant cholesterol; atherogenic index of plasma; carotid intima-media thickness

亚临床动脉粥样硬化(subclinical atherosclerosis)又叫临床前动脉粥样硬化(preclinical atherosclerosis, PCA),是指已有动脉粥样硬化(AS),而尚无重要动脉血管如冠状动脉、脑动脉、肾动脉及外周动脉等

严重动脉粥样硬化狭窄的临床症状。肥胖是亚临床 AS 的独立危险因素。近十年来儿童肥胖发病率迅猛上升,肥胖儿童患心脏病的概率比正常儿童高 3~5 倍,成年后心血管疾病患病率远远高于正常儿童。儿童肥胖诱发的血脂代谢异常是 AS 重要的危险因素。其中低密度脂蛋白胆固醇(LDL-C)与冠状动脉

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表2 肥胖组血脂指标与 AIP 的相关性分析

Tab 2 The relationship between the serum lipid parameters and AIP of obese group

血脂指标	R	P
TG	0.92**	0.00
TC	0.05	0.70
HDL-C	-0.65**	0.00
LDL-C	-0.11	0.38
non-HDL-C	0.30*	0.02
remnant cholesterol	0.57**	0.00

* 在 0.05 水平(双侧)上显著相关,** 在 0.01 水平(双侧)上显著相关

3 讨论

亚临床 AS 是 AS 的早期阶段,是临床心脑血管事件发生的必然阶段,常预示心脑血管疾病终点事件的危险性增高,因此早期诊断、早期干预是目前减少心血管疾病(CVD)的主要措施。已有研究表明 AS 始于儿童、婴幼儿甚至胎儿时期^[4-6],是一种小儿时期得病,成人期发病的疾病,在儿童时期尚处于临床上休眠状态(clinically dormant),直到斑块破裂或斑块侵蚀,进而导致血栓触发急性临床事件时才会被发现。颈动脉是 AS 的早期好发部位,是反映全身动脉粥样硬化斑块情况的理想敏感窗口,c-IMT 可作为亚临床 AS 的评价指标^[7]。Li 等^[8]的前瞻性研究发现儿童期具有心血管危险因素者,在其成人早期即可检测到 c-IMT 增加。鲍鹏丽等^[9]既往研究表明儿童肥胖后出现腹部脂肪聚集,腹部脂肪聚集可通过高胰岛素血症和胰岛素抵抗诱发高血压、血脂代谢异常和 2 型糖尿病等 CVD 的危险因素,本研究中肥胖组儿童双侧 c-IMT 均为 (0.058±0.008) cm,参照近期发表的北京市小儿 c-IMT 的正常参考值^[10],均较正常儿童的增厚,提示肥胖儿童已经处于亚临床 AS。本研究中 c-IMT 与肥胖儿童的 BMI 呈正相关,表明儿童肥胖是 AS 的一个危险因素,因此早期干预儿童肥胖对降低肥胖儿童成年后 CVD 罹患率是非常重要的。

Lamarche 等^[11]已经证明致密小颗粒 LDL-C (sdLDL-C)致 AS 更强烈,LDL-C 的直径每减少 0.65 nm,患者冠心病危险性就会增加 35%。Dobiasova 等^[12]在 2001 年通过大样本研究提出了 AIP 的概念,将其定义为 TG 与 HDL-C 比值的对数,作为一项新的血脂指标,AIP 与 LDL-C 的颗粒大小呈明显的负相关。本研究中,肥胖组儿童的 AIP 水平较对照组的升高,意味着 LDL-C 颗粒直径变小,那么 sdLDL-C 所占的比例就会升高,致 AS 的危险性就会升高。本研究中肥胖组儿童各项指标与 AIP 的相关分析

中,AIP 与 TG、non-HDL-C、non-(HDL-C+LDL-C)呈正相关,提示 TG、non-HDL-C、remnant cholesterol 对肥胖儿童的亚临床 AS 有重要作用;且当 TG≥2.3 mmol/L 时 AIP 水平明显升高,提示肥胖儿童的 AS 的风险就会增加。

早在 1998 年 Frost 等^[13]即提出了:non-HDL-C,即 TC-HDL-C,包括了 LDL-C、VLDL-C、IDL-C、脂蛋白(a)等所有致 AS 的血脂因素,可作为 AS 危险评估及临床应用的较好指标。Frontini 等^[14]通过超声对 c-IMT 进行测量,分析各项血脂指标与 c-IMT 的关系,发现 non-HDL-C 较其他脂蛋白能更好识别亚临床 AS。近年来国内外亦都有研究表明在成人 non-HDL-C 是较 LDL-C 评估和预测 CVD 更好的指标^[15-16];国内鲜见儿童 non-HDL-C 相关报道,近期有报道提示 non-HDL-C 能更好的预测肥胖儿童非脂性 CVD 的危险^[17]。本研究中,肥胖组儿童的 non-HDL-C 水平较正常组的升高,提示 non-HDL-C 亦可作为评估肥胖儿童亚临床 AS 的血脂指标,可由此探讨肥胖儿童亚临床 AS 的危险因素。

成人研究发现,部分 AS 疾病患者 LDL-C 水平处于合适范围^[18],也有部分患者经降脂治疗 LDL-C 降至 70 mg/dL 后,AS 病变仍在进展^[19],提示除 LDL-C 外,其他血脂指标也影响冠心病的临床终点。近年来,不少研究认为富含 TG 的脂蛋白(TGRLP)也有明显致 AS 作用,TGRLP 包括 VLDL-C 及其残粒、IDL-C、乳糜微粒及其残粒等^[20]。TGRLP 进入血液循环后,被脂肪组织、骨骼肌、心肌及其他部位毛细血管内皮细胞表面的脂蛋白脂酶(LPL)脂解,去除大量 TG 和载脂蛋白 C;并在胆固醇酯转移蛋白作用下,接收来自低密度脂蛋白和高密度脂蛋白的胆固醇酯和载脂蛋白 E (apolipoproteinE, apoE),形成比 TGRLP 更小更致密的颗粒,总称为 TGRLP 残粒又称 RLPs。国外有研究表明^[21] RLPs 可以穿过血管内皮屏障,运载的胆固醇较 LDL-C 运载的多 5~20 倍。重要的是,RLPs 不像 LDL-C,能在非修饰的状态下被内皮下的巨噬细胞吞噬摄取,从而增加了泡沫细胞的形成^[22]。Varbo 等^[3]研究表明,不管是否空腹状态,胆固醇均可由 RLPs 转运,RLPs 是冠状动脉疾病危险有力的预测指标,并提出 remnant cholesterol: non-(HDL-C+LDL-C)可作为缺血性心脏病重要的危险原因,不管 HDL-C 是否降低,remnant cholesterol 每提高 1 mmol/L (39 mg/dL),发生缺血性心脏病的危险就会增加 2.8 倍。Remnant cholesterol 包括乳糜微粒、VLDL-C、IDL-C 等,是富含 TG 的脂蛋白,可作为评估 TGRLP 的指标。肥胖儿童常伴有高胰岛

素血症和胰岛素抵抗,可使 LPL 活性下降,从而使 TGRLP 升高,最终可致 RLPs 升高。本研究中,肥胖组儿童 remnant cholesterol 的水平较对照组的升高,表明 TGRLP 在肥胖儿童已升高,且当 $TG \geq 2.3$ mmol/L 时 remnant cholesterol 水平明显升高,提示肥胖儿童的 AS 的风险就会增加。Remnant cholesterol 排除了 LDL-C 的影响,因此在调脂治疗中当 LDL-C 水平已明显下降或已达标,remnant cholesterol 可作为监测调脂疗效及预测 CVD 风险的新指标。

研究肥胖儿童的血脂谱特征,同时监测 c-IMT 观察肥胖儿童的亚临床 AS 发生及病变演变情况,不仅使治疗肥胖儿童的血脂紊乱有的放矢,还可以早期干预 AS 的危险因素。

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