·临床研究·

肥胖及2型糖尿病患者血清视黄醇结合蛋白4、脂联素与肿瘤坏死因子α水平变化及其相关性研究

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【摘 要】**目的** 检测肥胖及2型糖尿病患者血清视黄醇结合蛋白（RBP4）、脂联素及肿瘤坏死因子α（TNF-α）水平变化，探讨三者的相关性。**方法** 选择135例上海地区中国人，分为正常糖调节正常体质量（NBM-NGR）组、正常糖调节超重/肥胖（OW/OB-NGR）组、2型糖尿病正常体质量（NBM-T2DM）组及2型糖尿病伴超重/肥胖（OW/OB-T2DM）组，测定体脂、生化指标及RBP4、脂联素及TNF-α水平。**结果** T2DM各亚组及OW/OB-NGR组RBP4均显著高于NBM-NGR组，OW/OB-T2DM组RBP4显著高于NBM-T2DM组；T2DM各亚组及OW/OB-NGR组脂联素均显著低于NBM-NGR组；T2DM各亚组TNF-α均显著高于NBM-NGR组及OW/OB-NGR组。Spearman相关分析显示，RBP4与脂联素呈负相关，与TNF-α呈正相关，TNF-α与脂联素呈负相关（$P < 0.05$或0.01）。多元逐步回归分析显示，甘油三酯及腰臀比（WHR）是血清RBP4的独立相关因素；性别、甘油三酯、糖化血红蛋白（HbA1c）及高密度脂蛋白是血清脂联素的独立相关因素；HbA1c是血清TNF-α的独立相关因素。**结论** RBP4与腹内型肥胖的关系更为密切，而与血糖不相关；脂联素、TNF-α主要与糖代谢相关；RBP4与脂联素及TNF-α均相关。

【关键词】肥胖症；糖尿病，2型；视黄醇结合蛋白质类；脂联素；肿瘤坏死因子α

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Serum levels of retinol binding protein 4, adiponectin and tumor necrosis factor-alpha and their correlations in patients with obesity and type 2 diabetes mellitus

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【**Abstract**】 **Objective** To detect the serum levels of retinol binding protein 4 (RBP4), adiponectin and tumor necrosis factor-alpha (TNF-α) in the patients with obesity and type 2 diabetes mellitus (T2DM), and to explore their correlations. **Methods** A total of 135 Chinese individuals living in Shanghai area were divided into the subjects with normal glucose regulation and normal body mass (NBM-NGR), overweight or obese subjects with normal glucose regulation (OW/OB-NGR), T2DM with normal body mass (NBM-T2DM) and T2DM with overweight or obesity (OW/OB-T2DM). The body fat, biochemical indices and the serum levels of RBP4, adiponectin and TNF-α were determined. **Results** Serum RBP4 levels were significantly higher in the subjects with T2DM and OW/OB-NGR than in those with NBM-NGR, and also in those with OW/OB-T2DM than in those with NBM-T2DM. Serum adiponectin levels were significantly lower in those with T2DM and OW/OB-NGR than in those of NBM-NGR. Serum TNF-α levels were significantly higher in those with T2DM than in those with NBM-NGR and OW/OB-NGR ($P < 0.05$ or 0.01). Spearman analysis indicated that RBP4 was negatively correlated to adiponectin but positively to TNF-α, and TNF-α had a negative correlation with adiponectin ($P < 0.05$ or 0.01). Multiple stepwise regression analysis showed that triglycerides (TG) and waist-hip ratio (WHR) were the independent risk factors for RBP4. TG, sex, hemoglobin A1c (HbA1c) and high density lipid protein-cholesterol (HDL-C) were the independent risk factors for adiponectin. HbA1c was the independent risk factor for TNF-α. **Conclusion** RBP4 is closely associated with abdominal obesity, but has no correlation with blood glucose. Adiponectin and TNF-α are mainly related to glucose metabolism. RBP4 is related with adiponectin and TNF-α.

【**Key words**】 obesity; diabetes mellitus, type 2; retinol-binding proteins; adiponectin; tumor necrosis factor-alpha

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肥胖是糖尿病、血脂异常、高血压等多种疾病的危险因素[1]。研究发现，脂肪组织已成为一个功能活跃的内分泌器官，分泌多种细胞因子，如脂联素（adiponectin）、肿瘤坏死因子（tumor necrosis factor，TNF）等脂肪源性因子，而肥胖者的脂肪细胞肥大及数量增多，可导致脂肪源性激素的表达增强或减弱[2]。视黄醇结合蛋白4（retinol binding protein 4，RBP4）是一种新发现的脂肪细胞因子，主要由肝细胞和脂肪细胞分泌，影响胰岛素的敏感性，增加肝糖输出[3]。目前很多研究发现RBP4、脂联素、TNF-α脂肪细胞因子广泛参与了2型糖尿病（type 2 diabetes mellitus，T2DM）的病理过程。但是围绕RBP4、血清脂联素与TNF-α之间相互关系及其对肥胖及T2DM患者胰岛素抵抗的发生的影响研究不多，本研究对肥胖及T2DM患者RBP4、血清脂联素与TNF-α水平的变化及其相关性进行探讨。

1 对象与方法

1.1 对象

135例上海地区中国人，男69例，女66例，年龄20～69岁。按世界卫生组织（World Health Organization，WHO，1997）糖尿病诊断标准分为正常糖调节（normal glucose regulation，NGR）组及T2DM组；进一步按照WHO（1998）肥胖诊断标准分为4个亚组：正常糖调节正常体质量（normal body mass-normal glucose regulation，NW-NGR）组，正常糖调节超重/肥胖（overweight/obesity-normal glucose regulation，OW/OB-NGR）组，T2DM正常体质量（normal body mass-T2DM，NBM-T2DM）组，T2DM伴超重/肥胖（overweight/obesity-T2DM，OW/OB-T2DM）组。所有糖尿病患者均为新诊断且未接受任何治疗措施者，包括饮食、运动及药物治疗。排除标准：1型糖尿病患者，女性育龄患者（如服用避孕药者），皮质醇增多症等引起的继发性肥胖和糖尿病患者，酮症酸中毒者，以及伴有严重心、肝、肾功能不全患者。

1.2 方法

1.2.1 体脂测定 体质量指数（BMI）= 体质量/身高^2（kg/m^2），腰围（waist，肋骨下缘与髂嵴连线中点水平周径）、臀围（hip，臀部最大周径），腰臀比（waist-hip ratio，WHR）= 腰围/臀围。

1.2.2 生化指标检测 空腹（禁食8h）抽取静脉血，测定脂联素（双抗夹心法，美国Phoenix公司），批内变异系数（coefficient of variation，CV）3%～6%，批间CV < 10%；TNF-α（双抗夹心法，上海鑫乐生物科技有限公司）、RBP4（放射免疫法，美国Phoenix公司），批内CV < 8.5%，批间CV < 4.8%；空腹血糖（fasting plasma glucose，FPG，葡萄糖氧化酶法）、空腹胰岛素（fasting insulin，FINS，放射免疫法，美国LINCO公司）、糖化血红蛋白（glycosylated hemoglobin A1c，HbA1c，高压液相波谱法）；总胆固醇（total cholesterol，TC，葡萄糖氧化酶法）、甘油三酯（triglycerides，TG，甘油磷酸氧化酶法）、高密度脂蛋白胆固醇（high-density lipoprotein cholesterol，HDL-C）、低密度脂蛋白胆固醇（low-density lipoprotein cholesterol，LDL-C）由日立76002020生化自动分析仪完成（计算法）。HOMA-胰岛素抵抗指数（homeostasis model assessment-insulin resistance index，HOMA-IR）= FPG × FINS/22.5。

1.3 统计学处理

统计学处理使用SPSS17.0统计软件包进行。计量资料以$\bar{x} \pm s$表示。检验各组变量正态分布情况，非正态分布资料（如HOMA-IR）经对数转换后进行分析。两组间比较用方差分析及协方差分析。多因素分析采用Spearman相关及偏相关分析，多元逐步回归分析。以$P < 0.05$为差异有统计学意义。

2 结 果

2.1 一般临床资料比较

记录统计资料，各组例数分别为NBM-NGR组34例（男13例，女21例），OW/OB-NGR组38例（男22例，女16例），NBM-T2DM组27例（男15例，女12例），OW/OB-T2DM组36例（男19例，女17例），T2DM组63例（男34例，女29例）。如表1所示，各组间比较，T2DM组年龄最大。OW/OB-NGR、T2DM组的BMI、腰围显著高于NBM-NGR组；OW/OB-NGR组的腰臀比显著高于NBM-NGR组（$P < 0.05$或$P < 0.01$）。

2.2 临床生化资料比较

在糖代谢方面，T2DM各亚组及OW/OB-NGR组FPG均显著高于NBM-NGR组，T2DM各亚组FPG显著

表1 各组一般资料和实验室资料比较

Table 1 Comparison of general information and laboratory parameters among different groups ($\bar{x} \pm s$)

Item	NBM-NGR group	OW/OB-NGR group	NBM-T2DM group	OW-OB-T2DM group	T2DM group
Age(years)	41.15 ± 11.46	43.87 ± 11.89	50.96 ± 6.80$^{*\#}$	50.81 ± 10.12$^{*\#}$	50.87 ± 8.82$^{*\#}$
BMI(kg/m^2)	22.65 ± 2.07	28.89 ± 3.50*	22.02 ± 1.50$^{\#}$	29.58 ± 2.86$^{*\triangle}$	26.34 ± 4.45$^{*\#\triangle\blacktriangle}$
Waist(cm)	81.26 ± 8.27	95.75 ± 7.85*	81.23 ± 8.01$^{\#}$	90.86 ± 13.27$^{*\triangle}$	86.89 ± 12.20$^{*\#\triangle}$
WHR	0.86 ± 0.06	0.91 ± 0.05*	0.88 ± 0.08	0.87 ± 0.11	0.88 ± 0.10
FPG(mmol/L)	4.64 ± 0.56	5.17 ± 0.52*	7.92 ± 1.62$^{*\#}$	7.86 ± 1.78$^{*\#}$	7.89 ± 1.70$^{*\#}$
HbA1c(%)	5.21 ± 0.35	5.33 ± 0.40	7.82 ± 1.24$^{*\#}$	7.15 ± 1.04$^{*\#}$	7.45 ± 1.18$^{*\#}$
TC(mmol/L)	4.45 ± 0.93	4.87 ± 0.78	5.08 ± 1.09*	4.97 ± 0.90*	5.01 ± 0.98*
TG(mmol/L)	1.10 ± 0.59	1.82 ± 1.00*	1.42 ± 1.10	1.88 ± 1.08*	1.68 ± 1.10*
HDL-C(mmol/L)	1.35 ± 0.37	1.23 ± 0.27	1.28 ± 0.28	1.31 ± 0.38	1.30 ± 0.34
LDL-C(mmol/L)	2.68 ± 0.70	3.01 ± 0.61	3.12 ± 0.67*	3.07 ± 0.87*	3.09 ± 0.79*
Ln(HOMA-IR)	0.70 ± 0.26	1.26 ± 0.50*	1.06 ± 0.51*	1.53 ± 0.56$^{*\#\triangle}$	1.34 ± 0.58$^{*\triangle}$
FINS(μU/ml)	9.57 ± 2.62	19.65 ± 16.74*	14.66 ± 19.09	15.01 ± 7.35*	14.91 ± 13.62*
RBP4(μg/ml)	25.81 ± 6.03	29.65 ± 6.63*	28.26 ± 5.16*	31.94 ± 7.62$^{*\triangle}$	30.34 ± 6.86$^{*\triangle}$
Adiponectin(μg/ml)	28.95 ± 10.65	20.55 ± 8.35*	17.56 ± 9.48*	18.44 ± 7.98*	18.08 ± 8.54*
TNF-α(ng/L)	72.51 ± 18.25	79.75 ± 22.93	95.13 ± 36.13$^{*\#}$	101.80 ± 27.48*	98.92 ± 31.34$^{*\#}$

NBM: normal body mass; NGR: normal glucose regulation; OW: overweight; OB: obesity; T2DM: type 2 diabetes mellitus; BMI: body mass index; WHR: waist-hip ratio; FPG: fasting plasma glucose; HbA1c: hemoglobin A1c; TC: total cholesterol; TG: triglycerides; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; HOMA-IR: Homeostasis Model Assessment-insulin resistance index; FINS: fasting insulin; RBP4: retinol binding protein 4; TNF-α: tumor necrosis factor α. Compared with NBM-T2DM group, $^{*}P < 0.05$; compared with OW/OB-T2DM group, $^{\#}P < 0.05$; compared with NBM-NGR group, $^{\triangle}P < 0.05$; compared with OW/OB-NGR group, $^{\blacktriangle}P < 0.05$

高于OW/OB-NGR组；T2DM各亚组HbA1c显著高于NBM-NGR组及OW/OB-NGR组；FINS在OW/OB-NGR组最高，T2DM组及OW/OB-NGR组FINS高于NBM-NGR组；ln（HOMA-IR）在OW/OB-T2DM组最高，T2DM各亚组及OW/OB-NGR组ln（HOMA-IR）均显著高于NBM-NGR组（$P < 0.05$或$P < 0.01$）。在脂代谢方面，T2DM各亚组TC显著高于NBM-NGR组；T2DM组及OW/OB-NGR组TG显著高于NBM-NGR组；T2DM各亚组LDL-C均显著高于NBM-NGR组，各组间HDL-C差异无统计学意义（$P < 0.05$或$P < 0.01$）。

2.3 各组间血清RBP4、脂联素及TNF-α的比较

如表1所示，RBP4在OW/OB-T2DM组最高，T2DM各亚组及OW/OB-NGR组RBP4均显著高于NBM-NGR组，OW/OB-T2DM组RBP4显著高于NBM-T2DM组；校正性别、年龄后，OW/OB-T2DM组血清RBP4仍显著高于NBM-NGR组及NBM-T2DM组，差异有统计学意义（$P < 0.05$或$P < 0.01$），但OW/OB-NGR组、NBM-T2DM组及T2DM组与NBM-NGR组组间差异消失。T2DM各亚组及OW/OB-NGR组脂联素均显著低于NBM-NGR组；校正性别、年龄后，T2DM各亚组及OW/OB-NGR组与NBM-NGR组差异仍具有统计学意义（$P < 0.05$或$P < 0.01$）。TNF-α在OW/OB-T2DM组最高，T2DM各亚组TNF-α均显著高于NBM-NGR组及OW/OB-NGR组（$P < 0.05$或$P < 0.01$）；校正性别、年龄后，T2DM各亚组TNF-α与NBM-NGR组及OW/OB-NGR组差异仍具有统计学意义（$P < 0.05$）。

表2 血清RBP4、TNF-α、脂联素之间的Spearman分析

Table 2 Spearman analysis of RBP4, TNF-α and adiponectin

Parameter	RBP4	Adiponectin	TNF-α
Gender	−0.144	−0.475**	−0.126
Age	0.100	0.011	0.124
BMI	0.240**	−0.183*	0.193*
Waist	0.277**	−0.151*	0.088
WHR	0.316**	−0.187*	0.162*
FBG	0.126	−0.298**	0.279**
HbA1c	0.107	−0.344**	0.259**
TC	0.202**	−0.092	0.041
TG	0.438**	−0.402**	0.180*
HDL-C	−0.172*	0.446**	0.042
LDL-C	0.169**	−0.163*	−0.240
FINS	0.095	−0.101	−0.009
HOMA-IR	0.135	−0.243**	0.122
Adiponectin	−0.210**	—	−0.356**
RBP4	—	−0.210**	0.181*
TNF-α	0.181*	−0.356**	—

BMI: body mass index; WHR: waist-hip ratio; FPG: fasting plasma glucose; HbA1c: hemoglobin A1c; TC: total cholesterol; TG: triglycerides; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; HOMA-IR: Homeostasis Model Assessment-insulin resistance index; FINS: fasting insulin; RBP4: retinol binding protein 4; TNF-α: tumor necrosis factor α. $^{*}P < 0.05$; $^{**}P < 0.01$

2.4 各组RBP4、脂联素、TNF-α之间及其与血糖、血脂、HOMA-IR等的相关分析

如表2所示，RBP4与脂联素呈负相关，相关系数$r = -0.210$（$P < 0.01$），RBP4与TNF-α呈正相关，$r = 0.181$（$P < 0.05$），TNF-α与脂联素呈负相关，$r = -0.356$（$P < 0.01$）。

RBP4与BMI、腰围、WHR、TC、TG呈正相关，$r =$

0.240，0.277，0.316，0.202，0.438（$P<0.01$），与LDL-C呈正相关，$r=0.169$（$P<0.05$），与HDL-C呈负相关，$r=-0.172$（$P<0.05$）。校正性别、年龄后，RBP4与BMI、腰围、WHR、TC、TG仍具有相关性仍显著存在。

脂联素与性别、BMI、腰围、WHR、FPG、HbA1c、TG、LDL-C及HOMA-IR呈负相关，$r=-0.475$，-0.183，-0.151，-0.187，-0.298，-0.344，-0.402，-0.163，-0.243（$P<0.05$或$P<0.01$），与HDL-C呈正相关，$r=0.446$（$P<0.01$）。校正性别、年龄后，脂联素与BMI、FPG、HbA1c、TG、LDL-C、HDL-C及HOMA-IR仍具有相关性，但与腰围和WHR无相关性。

TNF-α与BMI、WHR、FPG、HbA1c、TG呈正相关，$r=0.193$，0.162，0.279，0.259，0.180（$P<0.05$或$P<0.01$）。校正性别、年龄后，TNF-α与HbA1c仍有相关性，但与BMI、WHR、FPG、TG无相关性。

2.5 血清脂联素、TNF-α、RBP4的多元线性逐步回归分析

分别以血清RBP4、脂联素、TNF-α为应变量，以年龄、性别、BMI、腰围、WHR、FPG、HbA1c、TC、TG、HDL-C、LDL-C、ln（HOMA-IR）和INS为自变量进行多元逐步回归分析，TG、WHR是血清RBP4独立相关因素（相关指数$r^2=0.262$，0.184，$P<0.05$）；性别、TG、HbA1c及HDL-C是血清脂联素的独立相关因素（相关指数$r^2=0.329$，-0.231，-0.247，0.238，$P<0.01$）；HbA1c是血清TNF-α独立相关因素（相关指数$r^2=0.285$，$P<0.01$）。

3 讨 论

本研究显示，OW/OB-T2DM组RBP4显著高于其他4组，Spearman相关分析表明，RBP4与性别及年龄无明显相关性，与BMI、WHR呈正相关，表明RBP4与腹内型肥胖的关系更为密切，这与贾伟平等[4]的研究一致，而肥胖患者进行有氧运动干预后，其RBP4水平也有所降低，提示有效控制体质量有助于降低RBP4水平[5]。血清RBP4与FPG和HbA1c均无显著相关性，提示其与血糖关系不大，而与TC、TG、LDL-C正相关，与HDL-C负相关，逐步回归分析也显示了TG是独立相关因素，提示RBP4可能参与了脂代谢的调节，这与吴海娅等[6]及Von Eynatten等[7]的研究一致。本组资料显示，RBP4与脂联素呈负相关，与TNF-α呈正相关。Choi等[8]和Perseghin等[9]的研究发现，在曾患妊娠糖尿病（gestational diabetes mellitus，GDM）的妇女及非糖尿病患者群中，RBP4与脂联素呈负相关，我们的研究与以上两项研究一致。但是本研究未发现RBP4与HOMA-IR相关，可能与我们的入组人群不同及样本量偏少有关。王芳等[10]通过对肥胖人群的研究发现，RBP4与TNF-α显著正相关，我们的研究与其一致，但是究竟是高分泌的TNF-α刺激RBP4分泌的增加，还是RBP4的高分泌影响TNF-α，还有待于进一步的研究。

本研究显示，T2DM和超重/肥胖患者的脂联素低于非肥胖正常糖耐量人群，Spearman相关分析表明，脂联素与性别呈正相关，性别间血清脂联素水平差异有统计学意义，女性血清脂联素水平显著高于男性，与很多研究一致[11]。脂联素与BMI、WHR呈负相关，提示脂联素减少与体脂增多有关，这与Hotta等[12]对日本人群的研究结果一致，Otabe等[13]应用转基因小鼠实验证明，脂联素能有效抵抗高脂饮食诱导的肥胖。而本实验进一步证明，血清脂联素浓度和直接代表体脂水平的WHR有着更强的负相关性。Weyer等[14]对患有肥胖和T2DM的Pima印第安人的研究表明，血清脂联素与FINS呈显著负相关，本研究未得出此结果，但与洪洁等[15]的研究一致。脂联素与FPG、HbA1c、HOMA-IR、TG及LDL-C呈负相关，与HDL-C呈正相关，提示脂联素调节糖脂代谢及胰岛素抵抗。我们的研究进一步支持了诸多研究的结论，脂联素不仅有抗动脉粥样硬化和调节糖脂代谢的生物学作用，而且在减轻胰岛素抵抗方面也发挥着不可忽视的作用[16,17]。

本组资料显示，T2DM各亚组TNF-α均显著高于NBM-NGR组及OW/OB-NGR组，以OW/OB-T2DM组TNF-α最高，但是T2DM各亚组内、NBM-NGR组与OW/OB-NGR组组间TNF-α差异无统计学意义，本研究未发现在超重/肥胖人群中TNF-α水平增高，多元逐步回归分析显示，HbA1c是血清TNF-α的独立相关因素，这与王权明等[18,19]的研究一致，表明TNF-α与糖尿病的关系更密切，进一步证明了非特异性炎症反应参与了T2DM的发病过程。本研究结果显示，脂联素与TNF-α呈显著负相关，这种负相关的原因可能是脂联素与炎症因子间的相互拮抗的生理作用。研究发现[20]：（1）脂联素能抑制脂肪组织生成TNF-α、对抗TNF-α对肌肉组织的不良反应、提高组织的胰岛素敏感性，呈剂量依赖性；（2）脂联素预防巨噬细胞转变成泡沫细胞，该转变是动脉粥样硬化的关键步骤[19]；（3）TNF-α可抑制脂肪细胞脂联素基因的表达[21]。这三者均表明了二者之间的拮抗关系。而这种拮抗关系可能是通过两种因子分别对胰岛素信号转导系统起正向调节和负向调节作用实现的。

本研究显示，WHR是血清RBP4独立相关因素，提示RBP4增多可能是由于腹内型肥胖所致，与血糖

不相关，RBP4可能不直接参与糖代谢；但是与甘油三酯呈独立相关，表明RBP4参与脂代谢过程。HbA1c是血清脂联素、TNF-α的独立相关因素，表明脂联素、TNF-α主要参与了糖代谢的调节；RBP4与脂联素及TNF-α均相关。本研究因样本量较小、相关系数较低，需要进一步研究证实。

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