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综 述

人体脂肪组织部位差异性与代谢综合征

王 冉，李晓南*

南京医科大学附属儿童医院儿童保健科，南京 210008

摘 要：肥胖主要表现为脂肪组织的过度聚集，而内脏脂肪组织的集聚与代谢综合征密切相关。不同部位脂肪组织在解剖学、脂肪细胞生物学、糖脂代谢和内分泌调节上存在显著差异。与皮下脂肪组织相比，内脏脂肪组织具有较强的代谢活性，产生大量游离脂肪酸、脂肪细胞因子、激素、炎症介质等直接进入肝脏及全身组织，这些特征可能是内脏性肥胖导致胰岛素抵抗、2型糖尿病、非酒精性脂肪肝、血脂紊乱等代谢综合征的重要机制，内脏脂肪组织成为临床监测、干预和治疗的靶标。

关键词：皮下脂肪组织；内脏脂肪组织；脂肪细胞因子；代谢综合征
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Different adipose tissue depots and metabolic syndrome in human

WANG Ran, LI Xiao-Nan*
Department of Child Health Care, Children's Hospital of Nanjing Medical University, Nanjing 210008, China

Abstract: Obesity is characterized by abnormal and excessive adipose tissue accumulated in the body. Compared with peripheral obesity (the accumulation of subcutaneous adipose tissue), abdominal obesity (the accumulation of visceral adipose tissue) is associated with increased risk of the metabolic syndrome, such as diabetes, hypertension, atherosclerosis, and dyslipidemia. Adipose tissue is a highly heterogeneous endocrine organ. Adipose tissue depots differ significantly in anatomy, cell biology, glucose and lipid metabolism as well as in endocrine regulation. Visceral adipose tissue has a stronger metabolic activity and secrets a larger amount of free fat acids, adipocytokines, hormones and inflammatory factors, which flux into the liver directly via the hepatic portal vein. These characteristics indicate that visceral adiposity may lead to the metabolic syndrome and thus visceral adipose tissue might be the clinical target for the prevention and treatment of obesity.

Key words: subcutaneous adipose tissue; visceral adipose tissue; depot-specific; metabolic syndromes

肥胖是指长期能量摄入超过消耗引起的一种慢性营养性疾病，与糖代谢紊乱、高血压、血脂异常等代谢综合征的发生密切相关[1–3]。流行病学调查表明，肥胖和代谢综合征已成为21世纪严峻的公共卫生问题[4]。尤其是儿童体重过重和肥胖人数呈迅速增加趋势，与年轻的成人心血管疾病的发生密切相关。肥胖主要表现为脂肪组织的过度积聚，包括皮下脂肪组织(subcutaneous adipose tissue, SAT)和内脏脂肪组织(visceral adipose tissue, VAT)，而不同部位的脂肪组织具有高度异质性。研究证明，VAT的积聚(腹型肥胖)与代谢综合征的发生更为密切相关[5, 6]，其病理生理机制一直是肥胖领域研究的热点和难点。本文将从脂肪组织解剖生理、发育过程、内分泌代谢和调控等方面阐述脂肪组织的部位特异性及其在代谢综合征发生、发展过程中的病理生理作用。

1 脂肪组织的分布和增殖分化

1.1 脂肪组织的分布特点与代谢综合征

脂肪组织分白色和棕色脂肪组织，棕色脂肪组

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*Corresponding author. Tel: +86-25-86862996; E-mail: xnli@njmu.edu.cn

织随着年龄的增加逐渐减少，因此，青少年及成人的脂肪主要是白色脂肪。白色脂肪组织包括 SAT 和 VAT。人体大约 80% 的脂肪组织为 SAT，主要分布于臀部、大腿、背部和前腹壁皮下，VAT 主要分布于腹腔脏器周围，包括网膜脂肪、肠系膜脂肪、生殖周脂肪、后腹膜脂肪、肾周脂肪等 [7, 8]。儿童期 SAT 较为丰满，VAT 含量非常有限，但青春期开始 VAT 逐步增加，并呈现性别差异，女性进入青春期后出现大腿、臀部及腹部 SAT 的聚集。而围绝经期，脂肪组织出现了重新分布，表现为 SAT 的减少及 VAT 的聚集增加。男性青春期发育时脂肪组织主要分布于腹部内脏周围。

临床研究显示，腹部 VAT 聚集引起的肥胖 (又称内脏性、中心性肥胖或腹型肥胖)，与胰岛素抵抗、高血压、血脂紊乱等密切相关 [5, 9]，而下肢、臀部等周围脂肪组织的聚集 (周围性肥胖) 不增加代谢性疾病的发生风险 [10, 11]。“肝门理论”可以部分解释脂肪分布差异造成的不同临床结局。分布于 VAT 的静脉通过丰富的门静脉系统，将内脏脂肪代谢产物游离脂肪酸 (free fatty acid, FFA) 和脂肪细胞因子 (adipocytokine) 直接引流入肝脏。FFA 输入的增多可引起肝脏的胰岛素抵抗；各种脂肪细胞因子通过产生炎症介质激活肝脏免疫功能，从而促进代谢综合征的发生、发展 [12]。而 SAT 通过体循环回流，进入上腔静脉或下腔静脉 [13]，代谢产物稀释，延缓其对肝脏代谢的压力。去除 VAT 的动物，确实可以在短期内提高胰岛素敏感性、减轻炎症，而去除 SAT 并不能改善代谢 [14]。临床上，肥胖者通过抽脂减肥减少 SAT 的体积，但不能提高胰岛素敏感性 [15]，反而导致内脏脂肪细胞进一步增大，甚至异位脂肪组织的聚集，加剧脂肪组织功能紊乱和代谢性疾病的发生 [16, 17]。由此说明，VAT 代谢是肥胖靶向治疗的重点。

基于腹型肥胖与代谢紊乱的关系，代表腹型肥胖的指标如腰围 (waist)、腰臀比 (waist-hip ratio, WHR)、腰围身高比 (waist-height ratio, WHtR) 的重要性逐渐凸显，已成为代谢综合征的独立危险因素 [18, 19] 和诊断标准。而儿童和青少年 WHtR 适宜界值对探讨肥胖儿童和青少年发生并发症的危险性更具有重要的临床意义 [20–22]。

1.2 白色脂肪组织增殖分化的特征和调控

白色脂肪组织由大量脂肪细胞及基质成分组成，基质成分中包括未分化的前脂肪细胞、成纤维细胞、炎症细胞、血管及神经组织等，脂肪组织的增长表现为脂肪细胞数目的增加、细胞的分化、体积的增大 [23]。脂肪细胞的增殖贯穿整个生命过程，伴随不同阶段生长发育特点表现不同。出生前 3 个月、生后第一年和 11~13 岁三个阶段是脂肪细胞增殖的关键期，这种脂肪细胞数目的增加是不可逆的。人类脂肪细胞动力学研究证明，肥胖儿童脂肪细胞数目明显高于正常儿童，并持续至成年期 [24]。因此，婴儿期及青春期是设定脂肪细胞数目的关键期，幼年期正常体型的儿童仅有不到 10% 发展为成年期肥胖，而肥胖儿童约 70% 持续肥胖至成年期 [25, 26]。至成年期前，脂肪细胞的增殖分化能力降低，主要通过脂肪细胞体积的增加储存能量。

脂肪细胞的增殖和分化受遗传、激素和营养等多种因素的调控，转录因子、细胞信号通路影响不同部位的脂肪组织的分化和增殖能力。类固醇激素如糖皮质激素、性激素调节脂肪细胞分化、脂质的聚集和脂肪的分布具有明显部位差异性 [27]。糖皮质激素可以增加 SAT 脂解作用，促进 VAT 前脂肪细胞分化、增强脂质合成通路最终促进 VAT 的聚集。而糖皮质激素活化酶 11β 羟基类固醇脱氢酶 (11β-hydroxysteroid dehydrogenase, 11βHSD1) 和糖皮质激素受体水平在 VAT 中表达和活性均显著高于 SAT，从而增加内脏脂肪细胞的分化和脂质积聚 [27–30]。雌激素受体主要分布于 SAT，可以促进脂肪组织向皮下分布 [31]，减少 VAT 中脂肪细胞的体积及数量。雄激素受体主要分布在 VAT 中，它可以抑制前脂肪细胞分化，但雄激素量不足时，则促使内脏脂肪细胞分化增殖，加重内脏脂肪体积 [32]。PPARγ 和 C/EBPα 是前脂肪细胞分化发育的重要调节因子 [33]，敲除小鼠脂肪组织中的 PPARγ 或 C/EBPα 后，其前脂肪细胞分化成熟能力明显下降。在人类，SAT 较 VAT 表达更高水平的 PPARγ 和 C/EBPα[34, 35]，前脂肪细胞具有更强的增殖、复制能力，能够抵抗 TNFα 诱导的脂肪细胞凋亡 [36]。而 VAT 前脂肪细胞则相反，对凋亡信号更敏感 [37, 38]。这些部位特征性调控参与了不同发育期脂肪组织的增生和分布。

2 脂肪组织代谢的部位差异

2.1 脂代谢的部位差异

研究显示，VAT 较 SAT 具有更强的脂代谢活性，两者在代谢相关的内分泌激素受体、激素敏感性、脂代谢相关酶的表达方面存在着显著的差异 (表 1)。

表1. 脂肪细胞表面代谢相关的受体、酶的部位差异性表达

Table 1. Receptors and enzymes expressed in different adipose tissues

	Depots difference	References
Receptors		
Catecholamine receptors		
β1, β2 receptors	VAT > SAT	[39–41]
α1, α2 receptors	SAT > VAT	[39–41]
Glucocorticoid receptor	VAT > SAT	[28]
Insulin receptor	SAT > VAT	[42]
Androgen receptor	VAT > SAT	[32]
Estrogen receptor	SAT > VAT	[31]
Enzyme for lipid metabolic		
11βHSD1	VAT > SAT	[28]

SAT: subcutaneous adipose tissue; VAT: visceral adipose tissue; 11βHSD: 11β-hydroxysteroid dehydrogenase.

内脏脂肪细胞膜上肾上腺素受体 β1、2、3 表达较高，因此对儿茶酚胺诱导的脂肪分解更敏感，而抗脂解作用的肾上腺素受体 α2 表达明显较低 [39–41]，即 VAT 更易脂解导致循环中 FFA 升高。内脏脂肪细胞表面的胰岛素受体水平明显低于皮下脂肪细胞，并且对胰岛素受体的亲和性下降，使得 VAT 对胰岛素介导的抗脂解作用下降 [42]。因此，腹型肥胖者，VAT 脂解产生大量 FFA，导致大量的 FFA 沉积于非脂肪组织，例如肝脏、肌肉、胰腺等。一方面，FFA 通过激活丝氨酸激酶促进胰岛素受体底物磷酸化抑制胰岛素信号通路的转导，降低肝脏、骨骼肌等组织对胰岛素的敏感性 [43]。另一方面，FFA 可以激活组织炎症反应 [44]，最终导致胰岛素抵抗、血脂紊乱、糖耐量受损，血糖调节障碍。

2.2 不同部位的脂肪组织对糖代谢的影响

不同部位的脂肪组织对糖代谢的影响不同，内脏脂肪细胞表面胰岛素受体分布较少，胰岛素受体底物蛋白 -1 的表达下降，胰岛素受体的亲和性下降，因此 VAT 对胰岛素敏感性低于 SAT，糖摄取及利用率低 [42]。而 VAT 分解产生的 FFA 进一步影响胰岛素信号通路，降低肝脏、骨骼肌对胰岛素的敏感性，抑制葡萄糖摄取和氧化，加重糖耐量受损及血糖调节障碍 [45]。针对 89 例肥胖男性进行口服葡萄糖耐量实验、胰岛素钳夹实验、MRI 检测，发现血糖水平与 VAT 面积成正相关，葡萄糖利用率与 VAT 面积呈负相关，在 VAT 恒定的情况下，SAT 的变化与葡萄糖代谢无相关性 [46]。

3 脂肪组织内分泌功能的差异

脂肪组织不仅是一个储能器官还是重要的内分泌器官，脂肪细胞及血管基质成分通过分泌各种细胞因子、活性酶和激素，以旁分泌 / 自分泌 / 内分泌形式，参与脂肪细胞的增殖和分化 [47]、调节食欲、能量平衡、免疫功能和糖脂代谢平衡 [48, 49]。更为重要的是，这些细胞因子的分泌也存在部位差异 (表 2)。

3.1 胰岛素敏感性相关因子

脂肪组织可以分泌多种细胞因子，调节局部脂肪组织及全身组织器官的胰岛素敏感性。脂联素 (adiponectin) 是经典的脂肪组织分泌的具有胰岛素增敏作用的脂肪因子，具有改善胰岛素敏感性、抗炎、抗凋亡、抗动脉粥样硬化等功能 [50–52]。大量研究显示，脂联素的分泌表达主要位于 SAT，在超重肥胖儿童中，VAT 中脂联素的表达显著低于 SAT [35]。日本的一项临床研究分析 2 024 名中年人血清脂联素的水平及其影响因素，发现循环中脂联素的水平与腰围、BMI、内脏脂肪含量呈显著负相关 [53]。另有研究显示，血清脂联素水平与空腹胰岛素水平、空腹血糖、葡萄糖耐量呈负相关，与胰岛素敏感性呈正相关 [54]。肥胖及糖尿病患者体重减轻后其血清脂联素水平增加，同时胰岛素敏感性改善 [55]。给肥胖老鼠注射脂联素后可显著改善胰岛素敏感性，提高葡萄糖代谢 [56]。

瘦素 (leptin) 是一种经典的脂肪细胞因子。研究显示，无论成人还是儿童，SAT 中瘦素的表达明显高于 VAT，是瘦素的主要来源，并且其表达量与 BMI、SAT 含量呈正相关 [30, 57]。生理浓度下瘦素可以刺激糖原分解、脂肪酸 β 氧化、增加肝脏葡萄糖输出，增强葡萄糖转运，提高胰岛素敏感性；作用于中枢可以调节能量摄入与消耗，维持体脂含量及代谢稳定 [58]。当瘦素抵抗发生 (瘦素水平过高) 反

表2. 腹型肥胖患者脂肪组织的内分泌功能及其部位差异

Table 2. Adipocyte-derived proteins with endocrine functions and the heterogeneity in different adipose depots

	Proteins	Depots difference
Factors for insulin sensitivity	Adiponectin, leptin, Nrg4	SAT > VAT[35, 51, 57, 67]
	Resistin	VAT > SAT[60]
Pro-inflammatory factors	IL-1β, IL-6, IL-18, TNFα, IFNγ, MCP-1	VAT > SAT[69, 70]
Anti-inflammatory factors	IL-10	SAT > VAT[68]
RAS system factors	Renin, AGT, ACE, AT1, AT2	VAT > SAT[86–88]
Coagulation system factor	PAI-1	VAT > SAT[85]
Factors for thermogenesis	UCP-1	SAT > VAT[77–80]
Adipocyte apoptosis	TNFα	VAT > SAT[37]
Adipocyte differentiation	PPARγ, C/EBPα	SAT > VAT[34]

SAT: subcutaneous adipose tissue; VAT: visceral adipose tissue; Nrg4: neuregulin 4; AGT: angiotensinogen; ACE: angiotensin converting enzyme; AT1: angiotensin-1; AT2: angiotensin-2.

而促进脂肪分解、破坏胰岛素信号通路、导致胰岛素抵抗的发生[59]。

抵抗素 (resistin) 是一种脂肪细胞因子，它可以作用于胰岛素各靶器官并影响胰岛素信号转导通路，并且上调促炎细胞因子的表达，使得葡萄糖耐量及胰岛素信号通路受损。人体 VAT 分泌的抵抗素水平比 SAT 高 250%[60]。在高脂饮食诱导的肥胖小鼠中，随着体重及血糖的升高，肥胖及胰岛素抵抗会相继出现，其血清抵抗素的水平也增高；而血清抵抗素水平与 BMI、腰围、胰岛素敏感性呈负相关[61, 62]，并与 2 型糖尿病密切相关[63]。

近期，又有新的调节胰岛素敏感性的脂肪细胞因子被发现，例如神经调节蛋白 4 (neuregulin 4, Nrg4)[64, 65]、asprosin[66] 等，这为防治肥胖及代谢综合征提供了新的思路，目前已有动物研究表明 SAT 中 Nrg4 的表达高于 VAT[67]，但是这些脂肪细胞因子在人体脂肪组织中的表达是否具有部位差异及其调控机制尚需进一步验证。

3.2 炎症因子

大量研究表明，脂肪组织可以分泌大量的炎症因子参与调节全身免疫功能，SAT 及 VAT 在免疫炎症及与代谢的关系上均存在着显著差别。SAT 分泌较多的抗炎细胞因子，如 IL-10，可以抑制炎症反应及炎症介质产生，维持代谢稳定。IL-10 预处理脂肪细胞可以有效地减轻巨噬细胞诱导的炎症和胰岛素抵抗的发生[68]。而 VAT 分泌更多的促炎细胞因子，包括 IL-1β，IL-6，IL-8，IL-18，IL-12，IFNγ，MCP-1，TNFα，C 反应蛋白 (C-reaction protein, CRP) 等[69, 70]。美国的一项研究检测 16 000 余例正常成年人血清 CRP 水平，发现 CRP 与 BMI 呈高度相关[71]。进一步深入研究结果显示，人体血清中 TNFα、CRP 的水平与腰围呈显著正相关，并与糖耐量及胰岛素敏感性呈负相关[72]。因此，应用非甾体类抗炎药 (水杨酸、阿司匹林) 可以显著抑制 TNF、IL-6 的产生，增加脂联素表达，改善 2 型糖尿病患者糖耐量[73, 74]；TNF 抑制因子 (英夫利西单抗) 可以特异性阻断 TNFα，提高胰岛素敏感性[75]。但是，这类药物也会导致免疫功能紊乱，增加感染及肿瘤的风险，在临床上应用于治疗肥胖及代谢综合征尚无足够依据。目前临床上主要致力于应用抗炎营养素改善肥胖者的全身代谢炎症状态，例如，临床研究发现肥胖的青少年 n3 不饱和脂肪酸的干预可降低空腹血糖、TNFα 水平及肝脏脂肪含量，并显著提高胰岛素敏感性[76]。

3.3 产热相关因子

棕色脂肪组织是一种特殊类型的脂肪，通过线粒体氧化呼吸链解耦连作用释放热能，其数目随着年龄的增加逐渐减少。但近年来大量研究显示在长期寒冷暴露、运动、应激等刺激下，大鼠及人体 SAT 会出现棕色样改变，即表现为单房的脂滴中散在分布小的多房脂滴，且产热基因 UCP-1 的表达增加[77–79]，白色脂肪棕色样变显著增加能量消耗及胰岛素敏感性，减轻体重，改善代谢。并且 SAT 具有较强的棕色样变活性[80]，而肥胖者 VAT 产生的大量促炎介质会抑制棕色样变的发生[81]。

因此，促进白色脂肪棕色样变可能为治疗肥胖提供新方向，最近的临床研究证明寒冷刺激可以改善 2 型糖尿病患者的胰岛素敏感性[82]，一些药物也用于动物和细胞实验以促进白色脂肪棕色样变，如交感神经激动剂、前列腺素、脑钠肽、甲状腺激素、

FGF21 等[83]。

3.4 其它

此外，脂肪组织还可以分泌一些蛋白活性因子参与调节全身凝血与纤溶系统及水盐代谢的平衡，这些活性因子的分泌也具有显著的部位差异 (表 2)。例如，肥胖者内脏脂肪分泌丰富的血浆纤溶酶原激活抑制物 -1 (plasminogen activator inhibitor-1, PAI-1)，可以促进血栓形成、动脉粥样硬化斑块破裂[84]，是肥胖者发生心血管疾病的独立危险因素[85]。而腹型肥胖者肾素 - 血管紧张素系统 (renin-angiotensin system, RAS) 活性增强，包括肾素 (renin)、血管紧张素原 (angiotensinogen, AGT)、血管紧张素转化酶 (angiotensin converting enzyme, ACE)、血管紧张素 -1 (angiotensin-1, AT1)、血管紧张素 -2 (angiotensin-2, AT2) 等，促进水钠潴留及血压的升高，同时引起肥胖相关的肾损害[86–88]。

4 临床应用前景

综上所述，VAT 和 SAT 在细胞增殖、分化、生理代谢和内分泌功能上存在明显的部位差异性，以 VAT 聚集为主的腹型肥胖更容易导致胰岛素抵抗、血脂紊乱、2 型糖尿病等代谢性疾病的发生，因此，研究脂肪组织部位特性可为治疗肥胖、代谢性疾病提供新的靶标，如脂肪发育关键期的调控、调节不同部位的脂肪组织的分布、减轻炎症、促进白色脂肪棕色样变以及脂肪细胞因子为靶向的治疗等，一些药物在动物及细胞水平已取得了大量的成果，但应用于临床尚需进一步验证，以脂肪组织的部位差异性的调控为研究目标将成为今后肥胖预防、干预和治疗的重要方向。

* * *

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参考文献

1 Khan A, Raza S, Khan Y, Aksoy T, Khan M, Weinberger Y, Goldman J. Current updates in the medical management of obesity. Recent Pat Endocr Metab Immune Drug Discov 2012; 6(2): 117–128.

2 Taylor JR, Dietrich E, Powell JG. New and emerging pharmacologic therapies for type 2 diabetes, dyslipidemia, and obesity. Clin Ther 2013; 35(1): A3–A17.

3 Fujioka K. Current and emerging medications for overweight or obesity in people with comorbidities. Diabetes Obes Metab 2015; 17(11): 1021–1032.

4 Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, Mullany EC, Biryukov S, Abbafati C, Abera SF, Abraham JP, Abu-Rmeileh NM, Achoki T, AlBuhairan FS, Alemu ZA, Alfonso R, Ali MK, Ali R, Guzman NA, Ammar W, Anwari P, Banerjee A, Barquera S, Basu S, Bennett DA, Bhutta Z, Blore J, Cabral N, Nonato IC, Chang JC, Chowdhury R, Courville KJ, Criqui MH, Cundiff DK, Dabhadkar KC, Dandona L, Davis A, Dayama A, Dharmaratne SD, Ding EL, Durrani AM, Esteghamati A, Farzadfar F, Fay DF, Feigin VL, Flaxman A, Forouzanfar MH, Goto A, Green MA, Gupta R, Hafezi-Nejad N, Hankey GJ, Harewood HC, Havmoeller R, Hay S, Hernandez L, Husseini A, Idrisov BT, Ikeda N, Islami F, Jahangir E, Jassal SK, Jee SH, Jeffreys M, Jonas JB, Kabagambe EK, Khalifa SE, Kengne AP, Khader YS, Khang YH, Kim D, Kimokoti RW, Kinge JM, Kokubo Y, Kosen S, Kwan G, Lai T, Leinsalu M, Li Y, Liang X, Liu S, Logroscino G, Lotufo PA, Lu Y, Ma J, Mainoo NK, Mensah GA, Merriman TR, Mokdad AH, Moschandreas J, Naghavi M, Naheed A, Nand D, Narayan KM, Nelson EL, Neuhouser ML, Nisar MI, Ohkubo T, Oti SO, Pedroza A, Prabhakaran D, Roy N, Sampson U, Seo H, Sepanlou SG, Shibuya K, Shiri R, Shiue I, Singh GM, Singh JA, Skirbekk V, Stapelberg NJ, Sturua L, Sykes BL, Tobias M, Tran BX, Trasande L, Toyoshima H, van de Vijver S, Vasankari TJ, Veerman JL, Velasquez-Melendez G, Vlassov VV, Vollset SE, Vos T, Wang C, Wang X, Weiderpass E, Werdecker A, Wright JL, Yang YC, Yatsuya H, Yoon J, Yoon SJ, Zhao Y, Zhou M, Zhu S, Lopez AD, Murray CJ, Gakidou E. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2014; 384(9945): 766–781.

5 Tchernof A, Despres JP. Pathophysiology of human visceral obesity: an update. Physiol Rev 2013; 93(1): 359–404.

6 Wassink AM, van der Graaf Y, van Haeften TW, Spiering W, Soedamah-Muthu SS, Visseren FL. Waist circumference and metabolic risk factors have separate and additive effects on the risk of future type 2 diabetes in patients with vascular diseases. A cohort study. Diabet Med 2011; 28(8): 932–940.

7 Wajchenberg BL. Subcutaneous and visceral adipose tissue: their relation to the metabolic syndrome. Endocr Rev 2000; 21(6): 697–738.

8 Arner P. Regional adipocity in man. J Endocrinol 1997; 155(2): 191–192.

9 Tang L, Zhang F, Tong N. The association of visceral adipose tissue and subcutaneous adipose tissue with metabolic risk factors in a large population of Chinese adults. Clin En-

docrinol (Oxf) 2016; 85(1): 46–53.
10 Kloting N, Fasshauer M, Dietrich A, Kovacs P, Schon MR, Kern M, Stumvoll M, Bluher M. Insulin-sensitive obesity. Am J Physiol Endocrinol Metab 2010; 299(3): E506–E515.
11 Porter SA, Massaro JM, Hoffmann U, Vasan RS, O'Donnel CJ, Fox CS. Abdominal subcutaneous adipose tissue: a protective fat depot? Diabetes Care 2009; 32(6): 1068–1075.
12 Gerner RR, Wieser V, Moschen AR, Tilg H. Metabolic inflammation: role of cytokines in the crosstalk between adipose tissue and liver. Can J Physiol Pharmacol 2013; 91(11): 867–872.
13 Item F, Konrad D. Visceral fat and metabolic inflammation: the portal theory revisited. Obes Rev 2012; 13 Suppl 2: 30–39.
14 Gabriely I, Ma XH, Yang XM, Atzmon G, Rajala MW, Berg AH, Scherer P, Rossetti L, Barzilai N. Removal of visceral fat prevents insulin resistance and glucose intolerance of aging: an adipokine-mediated process? Diabetes 2002; 51(10): 2951–2958.
15 Danilla S, Longton C, Valenzuela K, Cavada G, Norambuena H, Tabilo C, Erazo C, Benitez S, Sepulveda S, Schulz R, Andrades P. Suction-assisted lipectomy fails to improve cardiovascular metabolic markers of disease: a meta-analysis. J Plast Reconstr Aesthet Surg 2013; 66(11): 1557–1563.
16 Cox-York K, Wei Y, Wang D, Pagliassotti MJ, Foster MT. Lower body adipose tissue removal decreases glucose tolerance and insulin sensitivity in mice with exposure to high fat diet. Adipocyte 2015; 4(1): 32–43.
17 Benatti F, Solis M, Artioli G, Montag E, Painelli V, Saito F, Baptista L, Costa LA, Neves R, Seelaender M, Ferriolli E, Pfrimer K, Lima F, Roschel H, Gualano B, Lancha A Jr. Liposuction induces a compensatory increase of visceral fat which is effectively counteracted by physical activity: a randomized trial. J Clin Endocrinol Metab 2012; 97(7): 2388–2395.
18 Coutinho T, Goel K, Correa de Sa D, Kragelund C, Kanaya AM, Zeller M, Park JS, Kober L, Torp-Pedersen C, Cottin Y, Lorgis L, Lee SH, Kim YJ, Thomas R, Roger VL, Somers VK, Lopez-Jimenez F. Central obesity and survival in subjects with coronary artery disease: a systematic review of the literature and collaborative analysis with individual subject data. J Am Coll Cardiol 2011; 57(19): 1877–1886.
19 Ibrahim MM, Elamragy AA, Girgis H, Nour MA. Cut off values of waist circumference and associated cardiovascular risk in Egyptians. BMC Cardiovasc Disord 2011; 11: 53.
20 Ashwell M, Gibson S. Waist-to-height ratio as an indicator of 'early health risk': simpler and more predictive than using a 'matrix' based on BMI and waist circumference. BMJ Open 2016; 6(3): e010159.
21 Rivera-Soto WT, Rodriguez-Figueroa L. Is waist-to-height ratio a better obesity risk-factor indicator for puerto rican children than is BMI or waist circumference? P R Health Sci J 2016; 35(1): 20–25.
22 Sijtsma A, Bocca G, L'Abee C, Liem ET, Sauer PJ, Corpeleijn E. Waist-to-height ratio, waist circumference and BMI as indicators of percentage fat mass and cardiometabolic risk factors in children aged 3-7 years. Clin Nutr 2014; 33(2): 311–315.
23 Lemonnier D. Effect of age, sex, and sites on the cellularity of the adipose tissue in mice and rats rendered obese by a high-fat diet. J Clin Invest 1972; 51(11): 2907–2915.
24 Spalding KL, Arner E, Westermark PO, Bernard S, Buchholz BA, Bergmann O, Blomqvist L, Hoffstedt J, Naslund E, Britton T, Concha H, Hassan M, Ryden M, Frisen J, Arner P. Dynamics of fat cell turnover in humans. Nature 2008; 453(7196): 783–787.
25 Starc G, Strel J. Tracking excess weight and obesity from childhood to young adulthood: a 12-year prospective cohort study in Slovenia. Public Health Nutr 2011; 14(1): 49–55.
26 Clarke WR, Lauer RM. Does childhood obesity track into adulthood? Crit Rev Food Sci Nutr 1993; 33(4–5): 423–430.
27 Zhu L, Hou M, Sun B, Buren J, Zhang L, Yi J, Hernell O, Li X. Testosterone stimulates adipose tissue 11beta-hydroxysteroid dehydrogenase type 1 expression in a depot-specific manner in children. J Clin Endocrinol Metab 2010; 95(7): 3300–3308.
28 Rebuffe-Scrive M, Lundholm K, Bjorntorp P. Glucocorticoid hormone binding to human adipose tissue. Eur J Clin Invest 1985; 15(5): 267–271.
29 Macfarlane DP, Forbes S, Walker BR. Glucocorticoids and fatty acid metabolism in humans: fuelling fat redistribution in the metabolic syndrome. J Endocrinol 2008; 197(2): 189–204.
30 Li X, Lindquist S, Chen R, Myrnas T, Angsten G, Olsson T, Hernell O. Depot-specific messenger RNA expression of 11 beta-hydroxysteroid dehydrogenase type 1 and leptin in adipose tissue of children and adults. Int J Obes (Lond) 2007; 31(5): 820–828.
31 Rodriguez-Cuenca S, Monjo M, Proenza AM, Roca P. Depot differences in steroid receptor expression in adipose tissue: possible role of the local steroid milieu. Am J Physiol Endocrinol Metab 2005; 288(1): E200–E207.
32 Freedland ES. Role of a critical visceral adipose tissue threshold (CVATT) in metabolic syndrome: implications for controlling dietary carbohydrates: a review. Nutr Metab (Lond) 2004; 1(1): 12.
33 Evans RM, Barish GD, Wang YX. PPARs and the complex journey to obesity. Nat Med 2004; 10(4): 355–361.
34 Tchkonia T, Lenburg M, Thomou T, Giorgadze N, Frampton G, Pirtskhalava T, Cartwright A, Cartwright M, Flanagan J,

Karagiannides I, Gerry N, Forse RA, Tchoukalova Y, Jensen MD, Pothoulakis C, Kirkland JL. Identification of depot-specific human fat cell progenitors through distinct expression profiles and developmental gene patterns. Am J Physiol Endocrinol Metab 2007; 292(1): E298–E307.

35 Li X, Lindquist S, Angsten G, Yi J, Olsson T, Hernell O. Adiponectin and peroxisome proliferator-activated receptor gamma expression in subcutaneous and omental adipose tissue in children. Acta Paediatr 2008; 97(5): 630–635.

36 Tchkonia T, Giorgadze N, Pirtskhalava T, Thomou T, DePonte M, Koo A, Forse RA, Chinnappan D, Martin-Ruiz C, von Zglinicki T, Kirkland JL. Fat depot-specific characteristics are retained in strains derived from single human preadipocytes. Diabetes 2006; 55(9): 2571–2578.

37 Niesler CU, Siddle K, Prins JB. Human preadipocytes display a depot-specific susceptibility to apoptosis. Diabetes 1998; 47(8): 1365–1368.

38 Li X, Chen R, Lindquist S, Hernell O. Expression of cellular inhibitor of apoptosis protein-2 in human subcutaneous and omental adipose tissue. Int J Obes Relat Metab Disord 2004; 28(3): 352–356.

39 Hellmer J, Marcus C, Sonnenfeld T, Arner P. Mechanisms for differences in lipolysis between human subcutaneous and omental fat cells. J Clin Endocrinol Metab 1992; 75(1): 15–20.

40 Arner P, Hellstrom L, Wahrenberg H, Bronnegard M. Beta-adrenoceptor expression in human fat cells from different regions. J Clin Invest 1990; 86(5): 1595–1600.

41 Karpe F, Pinnick KE. Biology of upper-body and lower-body adipose tissue--link to whole-body phenotypes. Nat Rev Endocrinol 2015; 11(2): 90–100.

42 Wium C, Eggesbo HB, Ueland T, Michelsen AE, Torjesen PA, Aukrust P, Birkeland K. Adipose tissue distribution in relation to insulin sensitivity and inflammation in Pakistani and Norwegian subjects with type 2 diabetes. Scand J Clin Lab Invest 2014; 74(8): 700–707.

43 Capurso C, Capurso A. From excess adiposity to insulin resistance: the role of free fatty acids. Vascul Pharmacol 2012; 57(2–4): 91–97.

44 Glass CK, Olefsky JM. Inflammation and lipid signaling in the etiology of insulin resistance. Cell Metab 2012; 15(5): 635–645.

45 Varlamov O, Somwar R, Cornea A, Kievit P, Grove KL, Roberts CT Jr. Single-cell analysis of insulin-regulated fatty acid uptake in adipocytes. Am J Physiol Endocrinol Metab 2010; 299(3): E486–E496.

46 Ross R, Aru J, Freeman J, Hudson R, Janssen I. Abdominal adiposity and insulin resistance in obese men. Am J Physiol Endocrinol Metab 2002; 282(3): E657–E663.

47 Lehr S, Hartwig S, Sell H. Adipokines: a treasure trove for the discovery of biomarkers for metabolic disorders. Proteomics Clin Appl 2012; 6(1–2): 91–101.

48 Henry SL, Bensley JG, Wood-Bradley RJ, Cullen-McEwen LA, Bertram JF, Armitage JA. White adipocytes: more than just fat depots. Int J Biochem Cell Biol 2012; 44(3): 435–440.

49 Rosen ED, Spiegelman BM. What we talk about when we talk about fat. Cell 2014; 156(1–2): 20–44.

50 Ye R, Scherer PE. Adiponectin, driver or passenger on the road to insulin sensitivity? Mol Metab 2013; 2(3): 133–141.

51 Ruan H, Dong LQ. Adiponectin signaling and function in insulin target tissues. J Mol Cell Biol 2016; 8(2): 101–109.

52 Kwon H, Pessin JE. Adipokines mediate inflammation and insulin resistance. Front Endocrinol (Lausanne) 2013; 4: 71.

53 Okauchi Y, Kishida K, Funahashi T, Noguchi M, Ogawa T, Ryo M, Okita K, Iwahashi H, Imagawa A, Nakamura T, Matsuzawa Y, Shimomura I. Changes in serum adiponectin concentrations correlate with changes in BMI, waist circumference, and estimated visceral fat area in middle-aged general population. Diabetes Care 2009; 32(10): e122.

54 Lu HL, Wang HW, Wen Y, Zhang MX, Lin HH. Roles of adipocyte derived hormone adiponectin and resistin in insulin resistance of type 2 diabetes. World J Gastroenterol 2006; 12(11): 1747–1751.

55 Hotta K, Funahashi T, Arita Y, Takahashi M, Matsuda M, Okamoto Y, Iwahashi H, Kuriyama H, Ouchi N, Maeda K, Nishida M, Kihara S, Sakai N, Nakajima T, Hasegawa K, Muraguchi M, Ohmoto Y, Nakamura T, Yamashita S, Hanafusa T, Matsuzawa Y. Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. Arterioscler Thromb Vasc Biol 2000; 20(6): 1595–1599.

56 Shetty S, Kusminski CM, Scherer PE. Adiponectin in health and disease: evaluation of adiponectin-targeted drug development strategies. Trends Pharmacol Sci 2009; 30(5): 234–239.

57 Ugrinska A, Miladinova D, Trajkovska M, Zdravkovska M, Kuzmanovska S, Tripunoski T, Vaskova O. Correlation of serum leptin with anthropometric parameters and abdominal fat depots determined by ultrasonography in overweight and obese women. Pril (Makedon Akad Nauk Umet Odd Med Nauki) 2013; 34(1): 115–119.

58 Asilmaz E, Cohen P, Miyazaki M, Dobrzyn P, Ueki K, Fayzikhodjaeva G, Soukas AA, Kahn CR, Ntambi JM, Socci ND, Friedman JM. Site and mechanism of leptin action in a rodent form of congenital lipodystrophy. J Clin Invest 2004; 113(3): 414–424.

59 Korek E, Krauss H. Novel adipokines: their potential role in the pathogenesis of obesity and metabolic disorders. Postepy Hig Med Dosw (Online) 2015; 69: 799–810 (in Polish with English abstract).

60 Fain JN, Cheema PS, Bahouth SW, Lloyd Hiler M. Resistin

release by human adipose tissue explants in primary culture. Biochem Biophys Res Commun 2003; 300(3): 674–678.

61 Han J, Yakup K, Yuan Q, Xu S, Li C, Rigeli T, Yu Y, Shen CL, Yang S. Relationship between serum resistin level of Xinjiang Uygur and Han subjects with metabolic syndrome. Clin Lab 2015; 61(12): 1941–1946.

62 Takemoto K, Deckelbaum RJ, Saito I, Likitmaskul S, Morandi A, Pinelli L, Ishii E, Kida K, Abdalla M. Adiponectin/resistin levels and insulin resistance in children: a four country comparison study. Int J Pediatr Endocrinol 2015; 2015(1): 2.

63 Park HK, Ahima RS. Resistin in rodents and humans. Diabetes Metab J 2013; 37(6): 404–414.

64 Ma Y, Gao M, Liu D. Preventing high fat diet-induced obesity and improving insulin sensitivity through neuregulin 4 gene transfer. Sci Rep 2016; 6: 26242.

65 Wang GX, Zhao XY, Meng ZX, Kern M, Dietrich A, Chen Z, Cozacov Z, Zhou D, Okunade AL, Su X, Li S, Bluher M, Lin JD. The brown fat-enriched secreted factor Nrg4 preserves metabolic homeostasis through attenuation of hepatic lipogenesis. Nat Med 2014; 20(12): 1436–1443.

66 Romere C, Duerrschmid C, Bournat J, Constable P, Jain M, Xia F, Saha PK, Del Solar M, Zhu B, York B, Sarkar P, Rendon DA, Gaber MW, LeMaire SA, Coselli JS, Milewicz DM, Sutton VR, Butte NF, Moore DD, Chopra AR. Asprosin, a fasting-induced glucogenic protein hormone. Cell 2016; 165(3): 566–579.

67 Rosell M, Kaforou M, Frontini A, Okolo A, Chan YW, Nikolopoulou E, Millership S, Fenech ME, MacIntyre D, Turner JO, Moore JD, Blackburn E, Gullick WJ, Cinti S, Montana G, Parker MG, Christian M. Brown and white adipose tissues: intrinsic differences in gene expression and response to cold exposure in mice. Am J Physiol Endocrinol Metab 2014; 306(8): E945–E964.

68 Oliver E, McGillicuddy FC, Harford KA, Reynolds CM, Phillips CM, Ferguson JF, Roche HM. Docosahexaenoic acid attenuates macrophage-induced inflammation and improves insulin sensitivity in adipocytes-specific differential effects between LC n-3 PUFA. J Nutr Biochem 2012; 23(9): 1192–1200.

69 Koenen TB, Stienstra R, van Tits LJ, Joosten LA, van Velzen JF, Hijmans A, Pol JA, van der Vliet JA, Netea MG, Tack CJ, Stalenhoef AF, de Graaf J. The inflammasome and caspase-1 activation: a new mechanism underlying increased inflammatory activity in human visceral adipose tissue. Endocrinology 2011; 152(10): 3769–3778.

70 Booth A, Magnuson A, Foster M. Detrimental and protective fat: body fat distribution and its relation to metabolic disease. Horm Mol Biol Clin Investig 2014; 17(1): 13–27.

71 Visser M, Bouter LM, McQuillan GM, Wener MH, Harris TB. Elevated C-reactive protein levels in overweight and obese adults. JAMA 1999; 282(22): 2131–2135.

72 Kern PA, Ranganathan S, Li C, Wood L, Ranganathan G. Adipose tissue tumor necrosis factor and interleukin-6 expression in human obesity and insulin resistance. Am J Physiol Endocrinol Metab 2001; 280(5): E745–E751.

73 Anderson K, Wherle L, Park M, Nelson K, Nguyen L. Salsalate, an old, inexpensive drug with potential new indications: a review of the evidence from 3 recent studies. Am Health Drug Benefits 2014; 7(4): 231–235.

74 Goldfine AB, Fonseca V, Jablonski KA, Chen YD, Tipton L, Staten MA, Shoelson SE. Salicylate (salsalate) in patients with type 2 diabetes: a randomized trial. Ann Intern Med 2013; 159(1): 1–12.

75 Stanley TL, Zanni MV, Johnsen S, Rasheed S, Makimura H, Lee H, Khor VK, Ahima RS, Grinspoon SK. TNF-alpha antagonism with etanercept decreases glucose and increases the proportion of high molecular weight adiponectin in obese subjects with features of the metabolic syndrome. J Clin Endocrinol Metab 2011; 96(1): E146–E150.

76 Lopez-Alarcon M, Martinez-Coronado A, Velarde-Castro O, Rendon-Macias E, Fernandez J. Supplementation of n3 long-chain polyunsaturated fatty acid synergistically decreases insulin resistance with weight loss of obese prepubertal and pubertal children. Arch Med Res 2011; 42(6): 502–508.

77 Wu J, Bostrom P, Sparks LM, Ye L, Choi JH, Giang AH, Khandekar M, Virtanen KA, Nuutila P, Schaart G, Huang K, Tu H, van Marken Lichtenbelt WD, Hoeks J, Enerback S, Schrauwen P, Spiegelman BM. Beige adipocytes are a distinct type of thermogenic fat cell in mouse and human. Cell 2012; 150(2): 366–376.

78 Seale P, Conroe HM, Estall J, Kajimura S, Frontini A, Ishibashi J, Cohen P, Cinti S, Spiegelman BM. Prdm16 determines the thermogenic program of subcutaneous white adipose tissue in mice. J Clin Invest 2011; 121(1): 96–105.

79 Harms M, Seale P. Brown and beige fat: development, function and therapeutic potential. Nat Med 2013; 19(10): 1252–1263.

80 Seale P, Kajimura S, Yang W, Chin S, Rohas LM, Uldry M, Tavernier G, Langin D, Spiegelman BM. Transcriptional control of brown fat determination by PRDM16. Cell Metab 2007; 6(1): 38–54.

81 Koncarevic A, Kajimura S, Cornwall-Brady M, Andreucci A, Pullen A, Sako D, Kumar R, Grinberg AV, Liharska K, Ucran JA, Howard E, Spiegelman BM, Seehra J, Lachey J. A novel therapeutic approach to treating obesity through modulation of TGFbeta signaling. Endocrinology 2012; 153(7): 3133–3146.

82 Hanssen MJ, Hoeks J, Brans B, van der Lans AA, Schaart G, van den Driessche JJ, Jorgensen JA, Boekschoten MV, Hesselink MK, Havekes B, Kersten S, Mottaghy FM, van Marken Lichtenbelt WD, Schrauwen P. Short-term cold acclimation improves insulin sensitivity in patients with type 2 diabetes mellitus. Nat Med 2015; 21(8): 863–865.

83 Bonet ML, Oliver P, Palou A. Pharmacological and nutritional agents promoting browning of white adipose tissue. Biochim Biophys Acta 2013; 1831(5): 969–985.

84 Saksela O, Rifkin DB. Cell-associated plasminogen activation: regulation and physiological functions. Annu Rev Cell Biol 1988; 4: 93–126.

85 Shimomura I, Funahashi T, Takahashi M, Maeda K, Kotani K, Nakamura T, Yamashita S, Miura M, Fukuda Y, Takemura K, Tokunaga K, Matsuzawa Y. Enhanced expression of PAI-1 in visceral fat: possible contributor to vascular disease in obesity. Nat Med 1996; 2(7): 800–803.

86 Hall JE, do Carmo JM, da Silva AA, Wang Z, Hall ME. Obesity-induced hypertension: interaction of neurohumoral and renal mechanisms. Circ Res 2015; 116(6): 991–1006.

87 Goossens GH, Blaak EE, van Baak MA. Possible involvement of the adipose tissue renin-angiotensin system in the pathophysiology of obesity and obesity-related disorders. Obes Rev 2003; 4(1): 43–55.

88 Engeli S, Schling P, Gorzelniak K, Boschmann M, Janke J, Ailhaud G, Teboul M, Massiera F, Sharma AM. The adipose-tissue renin-angiotensin-aldosterone system: role in the metabolic syndrome? Int J Biochem Cell Biol 2003; 35(6): 807–825.