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Edorium J Nutr Diet 2015;1:9–12.
www.edoriumjournals.com/ej/nd

EDITORIAL OPEN ACCESS

Distinct abdominal adipose tissue depots: Are there differential contributions for cardiovascular disease risk?

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Obesity is a medical condition characterized by excess body fat accumulation in the adipose tissue (AT), especially in the white adipose tissue (WAT), to the extent that it may have a negative effect on health, leading to reduced life expectancy and/or increased health problems. It is one of the most prevalent non-communicable diseases and a major concern for public health worldwide, mainly due to its well-established relationship with other disturbances, such as insulin resistance and diabetes and cardiovascular diseases [1].

Cardiovascular disease (CVD) includes hypertension, atherosclerosis, heart disease, vascular disease, and stroke. Several of the high-risk factors for CVD result directly or indirectly from obesity and a malfunctioning adipose tissue: dyslipidemia, chronic inflammation and diabetes [2]. At cellular level, mitochondrial dysfunction could also contribute to CVD due to their role as targets and sources of reactive oxygen species (ROS), both in the formation of vascular lesions and in their involvement in the development of insulin resistance and T2DM [3].

A well-functioning adipose tissue with capacity to neutralize and store nutritional overload is therefore necessary to protect the body from peripheral insulin resistance. Two closely linked processes in adipose tissue are important for the development of metabolic disease: adipose tissue inflammation and adipose tissue hypertrophy [2].

In this context, recently, WAT has been identified as an endocrine organ, since produces and releases several peptide and non-peptide factors related to metabolic homeostasis. Physiologically, WAT tissue secretes a number of hormones and cytokines called adipokines, such as leptin, adiponectin, resistin, tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), plasminogen activator inhibitor-1 (PAI-1), monocyte chemoattractant protein-1 (MCP-1/CCL2), angiotensinogen, among others [4]. Also, WAT is immunologically dynamic, with a remarkable concentration of resident leukocytes, being macrophages the most abundant leukocytes and appear to be at the center of obesity-related inflammation [5].

Crosstalk between adipocytes and resident leukocytes allows these systems to coordinate available energy stores for survival during times of starvation and pathogen challenge. However, chronic overnutrition causes pathological expansion of WAT coupled to derangements that challenges AT function to regulate metabolic homeostasis [6]. These derangements are characterized by the adipocyte hypertrophy, immune cells infiltration and over-production of proinflammatory adipokines (e.g., TNF-α) [7], chemokines (e.g., monocyte chemoattractant protein (MCP1/CCL2) [8]; and proinflammatory fatty acids [9]. In addition, WAT from obese subjects has less capacity to increase the capillary network surrounding adipocytes, causing adipocyte hypoxia and necrosis [10]. This process is characterized by the presence of crown-like structures (CLS), such as macrophages surrounding necrotic adipocytes [11].

Overall, these events drive to alterations in leukocyte number and phenotype, thereby expanding the inflammatory environment within adipose tissue beds. Altered expression of pro- and anti-inflammatory factors produced by leukocytes acts reciprocally on adipocytes, perpetuating inflammation and dysfunction [12]. This WAT-dysfunction is considered a key mechanism leading to systemic metabolic complications such as low-grade inflammation, insulin resistance and dyslipidemia [13], which often precede several CVD [14].

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Received: 16 May 2015
Published: 02 July 2015

Therefore, it is now widely agreed that obesity is also a state of low-grade chronic inflammation [15]. This relationship was suggested by earlier observations of higher circulating levels of inflammatory proteins in obese individuals, but it is currently believed that inflammation originates locally in WAT as a consequence of excessive fat deposition, and that it later reaches the systemic circulation leading to the low-grade chronic inflammation [1].

In obese subjects, the risk of developing CVD is proportional to the obesity grade, especially visceral obesity. However, the presence of these disturbances varies widely among obese subjects [16]. It has been shown that in Americans, over 30% of obese are metabolically normal and near 23% of normal subjects have metabolic disturbances [17]. Indeed, different studies about metabolically normal obese (MNO) have been published. However, there is no uniform classification for this phenotype, which demands a consensus, since it reflects in a wide range in the obese population.

One of the hypotheses that could explain these differences in the cardiovascular risk referrers to the location of WAT, being abdominal fat accumulation more associated with than other anatomic regions. It has been thoroughly confirmed that the adipocytes of visceral adipose tissue (VAT) are more lipolytically active and promotes fatty acids releasing directly into the portal circulation, fat accumulation in the liver and this has been an important feature of the metabolic syndrome [18]. Indeed, epidemiological studies indicate that mainly abundance of VAT is related to development of type 2 diabetes mellitus and CVD, although these studies do not discriminate between distinct visceral fat depots [14].

In the intra-abdominal region, several AT-depots can be distinguished based upon anatomic location. Subcutaneous adipose tissue (SAT) is located underneath the skin and VAT surrounds organs. SAT is considered to be the least active AT-depot, with lower macrophage infiltration and adipokine secretion compared to VAT [19]. Recently, in order to unravel the mechanisms whereby AT dysfunction contributes to cardiovascular complications of obesity, accurate knowledge of depot-specific contribution is crucial. Accurate assessment of putative differences between distinct visceral fat depots requires analyses of distinct fat biopsies obtained from a single individual. Although differences between subcutaneous and one type of visceral fat has been broadly studied, data on the inflammatory profile of distinct abdominal AT-depots and its relationship with cardiovascular risk, by equal comparison, is scarce [18].

Distinct visceral fat depots can be distinguished, of which mesenteric adipose tissue (MAT) lines the surface of the intestine, omental adipose tissue (OAT) relates to the greater omentum, and periaortic AT (PAT) surrounds the abdominal aorta [20]. PAT is located just outside the adventitial layer, and capable of secreting adipokines, which can diffuse directly into the vascular wall and thereby contribute to atherogenesis [21]. VAT is considered a highly active secretory organ, and the direct release of VAT-derived adipokines into the portal vein might directly affect hepatic glucose and lipid metabolism [22].

Also, VAT has been further classified based on drainage, distinguishing "true" VAT depots, e.g., omental and mesenteric fat drained by the portal vein, from intra-abdominal ("non-visceral") depots, drained by the inferior vena cava, including perigonadal (parametrial in females, epididymal in males), retroperitoneal, and perirenal fat [23]. The portal theory suggests that elevated hepatic delivery of free fatty acids and proinflammatory cytokines drained from VAT via the portal vein, is responsible for insulin resistance and metabolic deterioration in obese individuals [24]. However, even with this delineation, studies using VAT are inconsistent in their choice of VAT depot. Different fat pads are often used interchangeably although distinct depots are reportedly unique in tissue dynamics (hypertrophic versus hyperplastic response to excess calories), adipokine release, hormonal responses, vascularization innervation, and abundance of non-adipocyte components [23, 25]. For example, MAT and OAT are often conjointly termed VAT, and considered one and the same depot. However, OAT secretes more abundant amounts of adipokines compared to MAT, while in MAT lipolysis activity as well as adipocyte necrosis is more prominent compared to OAT [24–26]. Such intrinsic differences between MAT and OAT indicate that these distinct abdominal VAT-depots might contribute differently to distinct cardiometabolic complications of obesity.

Therefore, due to this diversity, it is possible that individual fat pads play differential roles in the pathogenesis of CVD. However, less is known about the differential contribution of distinct VAT-depots to obesity-induced metabolic derangements. Considering that there are still few successful treatments for obesity, knowing distinct mechanisms by which distinct VAT depots might contribute to metabolic disturbances, is a key field of research, since from this knowledge, it can be developed more targeted therapeutic treatments for obesity and its cardiovascular complications.

How to cite this article

Esteves EA, Dias-Peixoto MF. Distinct abdominal adipose tissue depots: Are there differential contributions for cardiovascular disease risk? Edorium J Nutr Diet 2015;2:1–4.

Article ID: 100002N09EE2015

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doi:10.5348/N09-2015-2-ED-2

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Author Contributions

Elizabethe Adriana Esteves – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Marco Fabrício Dias-Peixoto – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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