



WHITE ADIPOTOPOGRAPHY: TOTI *VERSUS* TOFI, OR A HIDDEN *HOMO OBESUS*

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Abstract

The white adipose tissue is located in (i) two large depots - subcutaneously and abdominally -, which are well-visible, and (ii) multiple small depots, which are invisible without using imaging technologies (echography, computed tomography and alike). Small adipose depots are located around the heart, blood vessels, pancreas, ovaries, prostate gland, and lymph nodes, also in the breast. Recent imaging studies demonstrated the presence of four major subphenotypes in internal adipose tissue distribution: TOTI (thin outside, thin inside), FOFI (fat outside, fat inside), FOTI (fat outside, thin inside) and TOFI (thin outside, fat inside), the latter may be considered an “invisible” or hidden expression of *Homo obesus*. Current thinking indicates that body mass index over 20–25 kg/m² should be considered as a “classical” anthropometric criterion for overweight and/or obesity. Briefly, being lean outside does not mean you are not obese inside.

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Introduction

Obesity is globesity today

Admittedly, the accumulation of white adipose tissue was linked to obesity. This was known to Hippocrates, who stated that “sudden death, is more common in those who are naturally fat than in the lean”. Thomas Short’s book, *A Discourse Concerning the Causes and Effects of Corpulency* (1727), was the first monograph on obesity published in English. The adipocyte, firstly dubbed “fat vesicle”, was recognized as a specific cell type of adipose tissue by Hassall (1849).

Adipose tissue is also associated with various psychosocial imprints that have changed over the centuries: from a sign of wealth in the middle ages, to a Rubenesque celebration during the Renaissance, to fear and loathing in modern Hollywood (unless of course it is injected into the lips or other ‘cosmetically desirable’ locations) (1).

Among the noncommunicable diseases (NCD), obesity is the most prevalent human health disorder globally and, consequently, the term globesity has emerged recently. Obesity is a major risk factor for a large number of NCD such as cardiometabolic diseases (atherosclerosis, hypertension, type 2 diabetes, metabolic syndrome). According to the World Health Organization (WHO) these diseases account for most NCD deaths - 17.7 million people annually, followed by cancers (8.8 million) and respiratory diseases (3.9 million). Altogether, these diseases

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account for over 80% of all premature NCD deaths. Further, WHO's key facts updated October 2017 demonstrated the following: (i) worldwide obesity has nearly tripled since 1975, (ii) in 2016, more than 1.9 billion adults were overweight (BMI 25.0 - 29.9 kg/m²); of these over 650 million were obese (BMI over 30 kg/m²), (iii) 39% of adults aged 18 years and over were overweight in 2016, and 13% were obese, (iv) 41 million children under the age of 5 were overweight or obese in 2016, (v) over 340 million children and adolescents aged 5-19 were overweight or obese in 2016, and (vi) it is predicted that overweight and obese people may reach be 2.7 billion in 2025. Sadly, in the last few decades Bulgaria and Serbia are among the leading countries affected by this global health burden.

Obesity and adipose tissue

At its core, obesity may be briefly classified as an accumulation and inflammation of white adipose tissue (1, 2) and dysfunction of brown adipose tissue (3). Basic and translational studies on cardiometabolic diseases are associated with the “rediscovery” of a neglected tissue, the adipose tissue (4-9). It was recognized as a vital player not only in the control of lipid and energy balance, but also inflammation, immunity, reproduction as well as cardiovascular and neuronal homeostasis. Adipose tissue is a cellular and extracellular matrix assembly composed of adipocytes, fibroblasts, immune cells and matrix components, rich in sympathetic nerve fibers, blood vessels, and stem cells.

There are two major subtypes of adipose tissue, white adipose tissue (WAT) and brown adipose tissue (BAT). In human body, WAT is the major endocrine and paracrine system secreting more than 600 signaling proteins collectively termed *adipokines* (4-7), whereas BAT increases the energy expenditure realized by uncoupling respiration from ATP synthesis via uncoupling protein 1 (UCP1) expressed in the inner mitochondrial membrane of brown adipocytes, thus mediating a process known as thermogenesis (1, 3). Recently, the knowledge of WAT and BAT were enriched with their derivatives, namely *brite* (brown in white) adipocytes and *bruscle* (brown in skeletal muscle) adipocytes (BAT and its phenotypes being out of the scope of present *Dance round*).

White adipose tissue (“the great white whale”) (1) is located in (i) two large, well-visible sites, namely, the subcutaneous and abdominal depot, as well as in (ii) multiple small depots (4; Fig. 1), invisible without imaging technologies (echography, computed tomography and alike). Small adipose depots are located around the heart, blood vessels, pancreas, ovaries, prostate gland, and lymph nodes. These organs are subjected to the action of pro- and anti-inflammatory adipokines, the disbalance of their secretion being involved in the development of cardio-

metabolic diseases, polycystic ovarian syndrome, prostate and breast cancer, arrhythmogenic right ventricular dysplasia, and Alzheimer's disease (4, 6-14).

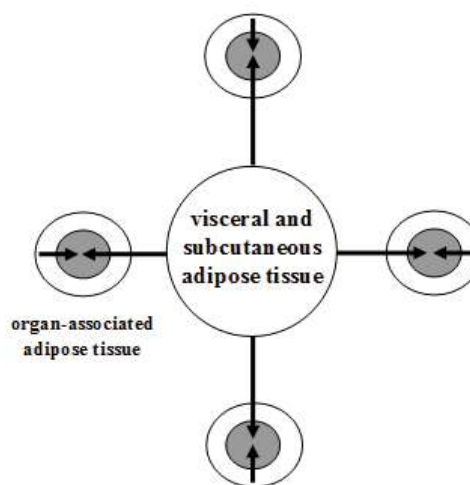


Figure 1. Schematic illustration of a large adipose depot (visceral and subcutaneous adipose tissue) and small adipose depots (organ-associated adipose tissue). Endocrine action (long arrows) and paracrine action (short arrows) of adipokines and of other adipose-derived signals on various organs. Organ parenchyma (grey) is surrounded by adipose tissue (white). From (4)

Paradigm shifts in the adipobiology of obesity

In 1962 Thomas S. Kuhn published his book *The Structure of Scientific Revolutions* (1st edition, University of Chicago Press, Chicago, USA). Its publication was a landmark event in history and philosophy of scientific knowledge (epistemology). Kuhn challenged the then prevailing view of “normal science” which was viewed as “development-by-accumulation” of accepted facts and concepts leading often to epistemological paralysis (neophobia). Kuhn argued for a model in which a period of such conceptual continuity in normal science were interrupted by a period of revolutionary science leading to a new paradigm, an event he designated *paradigm shift*. At epistemological level, the adipose tissue has undergone several paradigm shifts in the post-leptin era (i.e., last 23 years). This rise it above the horizon to take center stage in so many diseases that it leaves most scientists and medical doctors astonished.

The first paradigm shift in adipobiology states that while considered as passive storage-release of lipids by most cell biologists and pathologists for a long period of time, WAT is now consid-

ered the biggest endocrine and paracrine organ in the human body (4-9; Fig. 2).

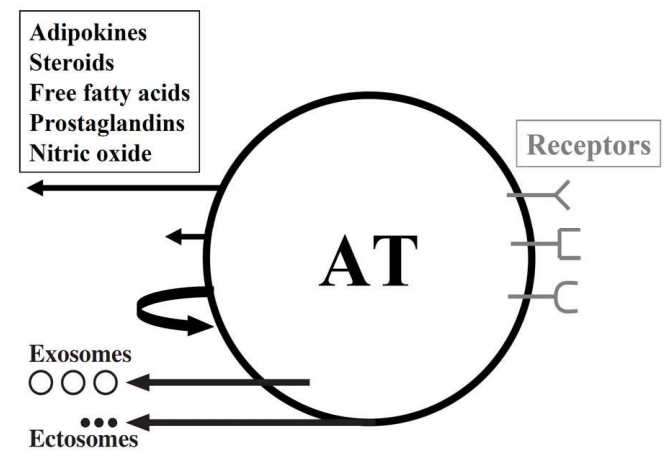


Figure 2. A drawing illustrating both secretory and receptor nature of adipose tissue (AT) cells. At the secretory level, AT-derived signaling molecules communicate via multiple pathways, such as endocrine (arrows 1, 4 and 5, from top to bottom), paracrine (arrow 2) and autocrine (arrow 3, curved). Also depicted is that AT cells express receptors for various ligands. From (9).

The heroes of the present Dance round

- (i) Jimmy Bell - Professor of Imaging and Molecular Medicine at the Center for Clinical Sciences, Hammersmith Hospital, Medical Faculty of the Imperial College in London, UK, and
 - (ii) the Little Prince - the most charming hero of the famous Antoine de Saint-Exupery, and
 - (iii) TOFI, TOTI, FOFI and FOTI.
- Good day - Jimmy Bell said.
- Good day - the Little Prince said.
- Good day - responded in choir TOFI, TOTI, FOFI and FOTI.
- JB:** The second paradigm shift in adipobiology of obesity derived from our study of scanned 477 volunteers with MRI technique, aimed at obtaining an internal map of WAT (15). In support of TOFI (thin outside, fat inside) subphenotype, we have demonstrated that as many as 45 percent of women and nearly 60 percent of men scanned have normal scores of the body mass index (BMI, 20–25 kg/m²). The subjects people were thin outside (TO), while actually have excessive levels of internal adipose tissue – they are fat inside (FI), hence TOFI phenotype of obesity. Noteworthy, TOFI was also found among professional models.
- LP:** The essential is invisible to the eyes. To remember it, the

Little Prince repeated: The essential is invisible to the eyes.

JB: Yes, TOFI is a Trojan horse in the human body, including elegant women - some models are also TOFI because they keep low-calorie diets but do not exercise.

LP: What should we do with our adipose tissue in order to have normal metabolism and healthy blood vessels?

JB: The white adipose tissue is the human body’s largest endo- and paracrine organ, secreting numerous adipokines.

LP: What should we do with our adipose tissue in order to have normal cardiometabolic homeostasis?

Since didn’t receive answer to his question, the Little Prince asked again.

JB: To eat low-calorie food, more fruits and vegetables, less salt - to be thin outside. To sport every day about 30 minutes of light running or fast walking - to be thin inside – in effect, that is, TOTI, a healthy phenotype of WAT.

LP: And you will see how everything changes. However, most politicians cannot ever understand how important it is, because their brains-and-hearts are obese.

Then TOFI, TOTI, FOFI and FOTI gave their business cards (16, Table 1) to ministers and other politicians, and showed them the financial costs of treating obesity-associated diseases – 145-210 billion of US dollars per year (17). Thus reminding them that “we are calling on politicians, health service providers, insurers and philanthropic organisations to prioritise investment in tackling obesity. This means investing in obesity research and therapy and early prevention.”

Table 1. Adipotopography (fat mapping): variations+

TOFI**	thin outside, fat inside
TOTI*****	thin outside, thin inside
FOFI*	fat outside, fat inside
FOTI**	fat outside, thin inside

+The number of asterisks indicates the quality of cardio-metabolic health, as related to adipotopography. Thus, TOTI represents a highest quality and FOFI - the lowest quality of cardiometabolic health. Therefore, stay TOTI. From (16).

Conflict of interest statement

The authors certify that they have no affiliations with or involvement in any organization with any financial interest in the subject matter discussed in the present *Dance Round*.

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