

## Diets and morbid tissues – history counts, present counts<sup>☆</sup>

Yaakov Henkin<sup>1†</sup>, Julia Kovsan<sup>2†</sup>, Yftach Gepner<sup>2</sup> and Iris Shai<sup>2\*</sup>

<sup>1</sup>Soroka University Medical Center, Beer-Sheva, Israel

<sup>2</sup>Department of Public Health, Faculty of Health Sciences, Ben-Gurion University of the Negev, PO Box 653, Beer-Sheva 84105, Israel

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### Abstract

Body fat distribution, especially visceral fat accumulation, may contribute more than total fat mass *per se* to the development of metabolic and cardiovascular disorders. Early prevention highly improves health outcomes later in life, especially when considering such cumulative conditions as atherosclerosis. However, as these processes emerge to be partly reversible, dietary and lifestyle interventions at any age and health condition are greatly beneficial. Given the worldwide abundance of metabolic and cardiovascular disorders, the identification and implementation of strategies for preventing or reducing the accumulation of morbid fat tissues is of great importance for preventing and regressing atherosclerosis. This review focuses on dietary strategies and specific food components that were demonstrated to alter body fat distribution and regression of atherosclerosis. Different properties of various adipose depots (superficial subcutaneous, deep subcutaneous and visceral fat depots) and their contribution to metabolic and cardiovascular disorders are briefly discussed. Visceral obesity and atherosclerosis should be approached as modifiable rather than ineluctable conditions.

**Key words:** Body fat distribution: Atherosclerosis: dietary strategies

By the early 1900s, it was well established that obesity has adverse health implications. Since then, our knowledge has come a long way. It was recognised that not all the fat tissues are identical and that upper-body and abdominal obesity is more pathogenic than lower-body and peripheral fat. Recently, the importance of fat distribution rather than total fat volume *per se* has been recognised, with special emphasis on the contribution of visceral fat accumulation to the development of metabolic and cardiovascular abnormalities. Moreover, the association between visceral adiposity and accelerated atherosclerosis has been shown to be independent of age, overall obesity and the quantity of subcutaneous fat<sup>(1)</sup>.

The ‘obesity epidemic’ that is emerging in industrialised as well as in developing countries around the world is threatening to compromise the impressive health achievements of the

past century<sup>(2–6)</sup>. A large number of diseases, the most important of which are related to insulin resistance (IR) and CVD, have been attributed to overweight and obesity states<sup>(7,8)</sup>. Given the worldwide prevalence of metabolic diseases and CVD, the identification of strategies and modifiers that may favourably alter the body fat distribution, reducing the morbid fat tissues and diminishing atherosclerosis, is of great importance to the development of more effective prevention and treatment approaches.

### Fat tissues

Body fat has long been recognised as an important contributor to the physiological and pathological function of the human body<sup>(9)</sup>. While it serves as an important depot for storage of

**Abbreviations:** BAT, brown adipose tissue; CHO, carbohydrate; IR, insulin resistance; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

\* **Corresponding author:** Dr I. Shai, fax +972 8 647 7637/8, email irish@bgu.ac.il

† Both authors contributed equally to this work.

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energy required in conditions of food shortage and starvation, the excessive accumulation of fat can also lead to undesirable effects. Fat depots in different parts of the body seem to have differential effects on metabolic abnormalities; while some have been shown to have detrimental effects and are associated with an increased risk for IR, diabetes mellitus and CVD, others are assumed to be neutral and possibly even protective against these conditions<sup>(9,10)</sup>. Similarly, different treatment modalities can have diverse effects on the various fat depots.

Adipocytes are organised in adipose tissue, a multidepot organ consisting of small blood vessels, nerve tissue, fibroblasts and adipocyte precursor cells in addition to mature adipose cells. The latter exist as two cytotypes, white and brown adipocytes, which can be distinguished by differences in their colour, histological appearance and function. Lipids are organised as multiple, small droplets in brown adipocytes and as a single, large lipid droplet in white adipocytes<sup>(11,12)</sup>.

### *Anatomy of fat tissues*

Humans have the highest percentage of fat per body mass among mammals<sup>(13)</sup> and have ten times more fat cells than expected for an animal of our size<sup>(14)</sup>. The capacity to accumulate fat has been a major adaptive feature of our species, but in the modern environment where fluctuations in energy supply have been minimised and productivity is dependent on mechanisation rather than physical effort, it becomes increasingly maladaptive.

Both adipocyte number and size determine the fat mass: the expansion of fat mass through increasing the number of adipocytes is termed 'hyperplasia', while increasing the average fat cell volume is termed 'hypertrophy'. Hypertrophy, i.e. increased fat storage in fully differentiated adipocytes resulting in enlarged fat cells, is well documented and is thought to be the most important mechanism whereby fat depots increase in adults<sup>(15,16)</sup>. The number of adipocytes is determined during childhood and adolescence and remains constant in adulthood, even after marked weight loss. However, approximately 10% of fat cells are renewed annually at all adult ages and levels of BMI, as was established by analysing the integration of <sup>14</sup>C derived from nuclear bomb tests in genomic DNA<sup>(17)</sup>.

**White fat.** Body fat is generally categorised as lower body adipose tissue, upper-body subcutaneous adipose tissue (SAT) and intra-abdominal/visceral adipose tissue (VAT)<sup>(10)</sup>.

Abdominal adipose tissue is composed of several distinct anatomical depots<sup>(18,19)</sup>:

**Subcutaneous adipose tissue.** SAT accounts for approximately 80% of total body fat and can be subdivided into superficial and deep layers<sup>(20)</sup>, separated by the fascia superficialis. We<sup>(20)</sup> recently suggested that the abdominal SAT is composed of two subdepots that associate differently with cardiometabolic parameters and that higher absolute and relative distribution of fat in abdominal superficial SAT may signify beneficial cardiometabolic effects in patients with type 2 diabetes.

**Intra-abdominal fat.** Intra-abdominal fat accounting for 10–20% of total fat in men and 5–8% in women can be

further subdivided into VAT or intraperitoneal adipose tissue, mainly composed of omental and mesenteric fat<sup>(21,22)</sup> and retroperitoneal fat.

Many factors are involved in the control of body fat distribution, the most important of which are age, sex, ethnicity, cigarette smoking, genetic factors and the timing of onset of childhood obesity<sup>(9,10,23)</sup>. The absolute as well as relative amount of visceral fat increases with age<sup>(24,25)</sup>. Women have more fat than men, even when matched for BMI, as a result of greater SAT deposits<sup>(26)</sup>. Men are found to have a greater proportion of fat in the VAT and deep SAT, while women have more in the superficial SAT depot<sup>(27)</sup>. A number of studies have shown that body fat distribution varies between populations, with individuals from south-east Asia having larger relative proportions of abdominal fat than Europeans and Americans<sup>(9,19)</sup>. Genetic studies show that a large proportion of the variance in abdominal fat mass can be accounted for by genetic factors<sup>(23,28,29)</sup>.

**Brown fat.** In neonates and newborn children, brown adipose tissue (BAT) can be found in several areas, including the interscapular region, surrounding blood vessels, neck muscles, axillae, trachea, oesophagus and around various abdominal and retroperitoneal organs. In adults, these brown adipocytes undergo a morphologic transformation in which they rapidly accumulate lipids, become unilocular and lose the ultrastructural and molecular properties that define them and regress<sup>(11)</sup>. As a consequence, there are no discrete collections of BAT that can be found in the adult. However, clinical studies using fluorodeoxyglucose positron emission tomography and computed tomography demonstrate that healthy adult humans have significant depots of metabolically active BAT, especially in the neck and upper-chest regions. Noradrenergic stimuli, such as cold exposure, can activate BAT and expand its positron emission tomography detectable signals in adult humans. The presence of BAT inversely correlates with body fat, especially in older subjects<sup>(30–33)</sup>.

### *Physiological and pathophysiological aspects of body fat*

Adipose tissue acts as the major energy storage depot<sup>(18)</sup>. The type of adipocytes, endocrine and metabolic function, and response to insulin and other hormones differ between SAT and VAT. Although VAT appears to store more dietary fat per gram of adipose tissue than either upper-body or lower-body SAT, the latter act as the major storage depot postprandially due to their larger depot size<sup>(10,34)</sup>. When the storage capacity of SAT is exceeded or its ability to generate new adipocytes is impaired, fat begins to accumulate in other depots. VAT has a higher rate of insulin-stimulated glucose uptake, meaning a higher turnover of lipids compared with SAT adipocytes<sup>(10,19)</sup>. Although the VAT depot is relatively small compared with SAT, the fact that it is more lipolytically active and that it releases NEFA directly to the liver through the portal vein raised the speculation that VAT-released NEFA would have a greater effect on hepatocyte metabolism than SAT-released NEFA. Nielsen *et al.* determined the relative contributions of NEFA released from visceral fat into the portal

and systemic circulations in lean and obese participants<sup>(35)</sup>. Although the relative contribution at any individual fat mass was quite variable, the relative amount of portal vein NEFA derived from visceral fat (approximately 5% in lean individuals and 20% in obese subjects) was generally much less than the relative amount of NEFA derived from lipolysis of the larger SAT depot. Although the latter are initially released into the systemic circulation, they are subsequently transported to splanchnic tissues by the arterial circulation, and the majority finally enter the portal vein. However, as the release of NEFA into the portal vein from lipolysis in VAT increases with increasing amounts of abdominal fat in obese individuals, the contribution of NEFA derived from VAT to the portal and systemic circulations increases with increasing adiposity<sup>(35,36)</sup>.

White adipose depots act as an active endocrine and paracrine organ and can influence appetite, energy balance, insulin sensitivity and other metabolic parameters. With increased adiposity, endocrine and paracrine function is significantly altered, and multiple adipocyte-derived factors induce activation and infiltration of macrophages into adipose tissue. Inflamed fat in obesity secretes an array of proteins implicated in the impairment of insulin signalling<sup>(37)</sup>. Several studies found that omental macrophage infiltration seems to be more prevalent than subcutaneous fat infiltration, especially with intra-abdominal obesity, and is correlated with weight circumference and with the number of metabolic syndrome parameters<sup>(18,38,39)</sup>.

The relationship between excess abdominal fat mass and IR was recognised in the 1940s when Vague<sup>(40)</sup> reported an association between an android (upper-body) obesity phenotype and diabetes, gout and premature atherosclerosis. This association is apparent even in individuals who are not obese by BMI criteria<sup>(41)</sup>. Basal whole-body NEFA flux rates are greater in upper-body obese subjects than in lower-body obese and lean subjects<sup>(42)</sup>. However, there is still some controversy regarding the relative contribution of each of these depots to the aetiology of the metabolic dysfunction observed in abdominally obese subjects, with conflicting results observed in different studies. Whereas some have shown VAT to be the major determinant of IR<sup>(43–46)</sup>, others found SAT to be equally (or possibly more) important in causing IR at the hepatic as well as muscle level<sup>(22,47–49)</sup>. This discrepancy may be related to the strong correlation between the subcutaneous and intra-abdominal depot size<sup>(50)</sup>, as well as to the different properties of the superficial and deep subcutaneous layers, the latter behaving more like VAT<sup>(51–53)</sup>.

BAT evolved in mammals to dissipate chemical energy as heat and thus possess large numbers of mitochondria that contain a unique protein called uncoupling protein 1<sup>(32)</sup>. This uncouples mitochondrial oxidative phosphorylation to dissipate heat instead of ATP synthesis. The sensation of cold causes sympathetic nerves to release catecholamines that stimulate proliferation and heat production by brown fat cells<sup>(54)</sup>. It has been suggested that BAT plays an essential role in energy balance, thus influencing body weight, and that increasing the amount and/or function of this tissue could be an effective therapy to limit obesity<sup>(32)</sup>. It has also

been shown that BAT activity induced by short-term cold exposure accelerates plasma clearance of TAG and glucose disposal, thus possibly affecting the metabolic disturbances associated with the metabolic syndrome<sup>(55,56)</sup>.

### Can diet affect body fat distribution?

VAT is more sensitive to weight reduction than SAT<sup>(18)</sup>, in relation to the initial volume of these fat depots, and most forms of weight loss appear to affect visceral fat more than subcutaneous fat<sup>(57)</sup>. The relative percent change in VAT to the percent change in total body fat appears to increase with increasing baseline VAT, suggesting that individuals with greater visceral fat mass lose more visceral fat when adjusted to the loss of body fat. Chaston & Dixon<sup>(58)</sup> performed a systematic review of the literature to look for factors associated with preferential loss of VAT relative to SAT during weight loss. They found that greater percent weight loss was negatively associated with the preferential loss of VAT compared with SAT ( $\% \Delta \text{VAT} / \% \Delta \text{SAT}$ ), suggesting that while modest weight loss generated preferential loss of VAT, greater weight loss attenuates this effect. Although the specific weight loss strategy did not significantly affect the differential loss of the various fat depots, very-low-energy diets provided an exceptional short-term (4 weeks) preferential VAT loss, which was attenuated after 12–14 weeks. Hall & Hallgreen<sup>(59)</sup> found support for these findings using an allometric model. Epicardial fat is also reduced by weight loss resulting from energy restriction<sup>(60)</sup>. However, less is known about the effect of specific dietary strategies or dietary components on fat tissue deposition.

### Dietary strategies

It is questionable whether not only the energy intake but also the specific dietary components, and their relative proportion in the diet, may affect the changes in body fat distribution. Carbohydrate (CHO) content might have a putative influence. A low-energy low-CHO diet (4184 kJ/d (1000 kcal/d), 39% energy from CHO) was found to preferentially reduce VAT and the VAT:SAT ratio more than a similar low-energy diet with a high-CHO content (62% energy from CHO) in twenty-two diabetic patients over 4 weeks<sup>(61)</sup>. A high-CHO diet (65% CHO, 6% SAT and 8% MUFA) increased the accumulation of fat deposited in the trunk depot and decreased in the amount of fat mass deposited in the legs compared with high-monounsaturated fat diet (47% CHO, 9% SAT and 23% MUFA) and a high-saturated fat diet (47% CHO, 23% SAT and 9% MUFA) among eleven insulin-resistant individuals during 28 d in a crossover design trial<sup>(62)</sup>. A study among sixteen participants, using 49% CHO (*v.* 44% in a control diet and 40% in a high-monounsaturated fat diet) also showed a disproportionate loss of lower-body fat resulting in an increase in the upper-body:lower-body fat ratio<sup>(63)</sup>. Nevertheless, the CHO effect might be dependent on accompanying dietary composition. Thus, when combined with a high-fibre intake, a low-fat, high-complex CHO during 12 weeks of diet (18% fat, 63% CHO and 26% of fibre per

4184 kJ (1000 kcal)) resulted in more substantial reduction in body weight and a higher percentage of body fat and thigh fat area loss than a high-fat, low-fibre, low-CHO diet (41% fat, 45% CHO and 7 g of fibre/4184 kJ (1000 kcal)) in thirty-four individuals with impaired glucose tolerance<sup>(64)</sup>. A high-protein diet (high dairy protein diet: 30 and 15% of total energy, respectively), associated with energy restriction and aerobic exercise, produced a greater decrease in total fat, VAT and trunk fat and gained more lean mass than an adequate total protein, low-dairy protein diet (15% and <2% of total energy, respectively) with similar energy intake and exercise in ninety healthy, premenopausal, overweight and obese women over 16 weeks. The reduction in VAT in all groups was correlated with intakes of Ca and protein<sup>(65)</sup>. A very-low-fat diet (12% energy from fat) and a high-monounsaturated fat diet (35% energy from fat, 20% energy from monounsaturated fat) that was equal in total energy content showed equal reductions in weight, total fat mass and total abdominal fat among sixty-two women during 12 weeks<sup>(66)</sup>. Currently, a longer and larger randomised controlled trial (the CENTRAL) using MRI for quantifying the various body fat depots is currently being conducted by our group to address the long-term dynamic re-distribution of various body fat depots following different dietary interventions.

#### Specific dietary components

Several studies suggest that not only the overall dietary strategies but also some specific dietary constituents have a major influence on body fat distribution and related metabolic abnormalities. For example, observational studies show inverse associations between whole-grain intake and intra-abdominal fat<sup>(67,68)</sup>, while several intervention trials suggest that green tea (apparently due to its polyphenol content, in particular catechins) decreases total and subcutaneous abdominal fat areas and results in a non-significant decrease in intra-abdominal fat area compared with a control beverage<sup>(69)</sup>. Novel 'functional foods' are still being addressed. Furthermore, consumption of different constituents, even from the same macronutrient group, may result in divergent effects on fat distribution. Thus, specific effects on body fat distribution were described for fructose. In rats, a fructose-rich diet consumed for 8 weeks resulted not only in increased visceral fat depots but also in functional derangement of both visceral and subcutaneous abdominal adipose tissues compared with rats fed a control diet in which the major sources of CHO consisted of starch and sugar. Lipid profile and plasma insulin levels were also adversely affected compared with controls<sup>(70)</sup>. Similarly, rats drinking fructose-enriched drinking-water exhibited a greater weight gain and greater total and VAT volumes, as well as more hypertriglyceridaemia than those drinking tap water alone<sup>(71)</sup>. Interestingly, a high-sucrose diet consumed for 20 weeks induced greater VAT accumulation without increasing body weight, in addition to a deranged lipid profile, IR and steatosis, resulting in an 'abdominally obese and normal-weight' rat model<sup>(72)</sup>. In humans, fructose-sweetened beverages were

also demonstrated to increase VAT in overweight/obese adults compared with glucose-sweetened beverages<sup>(73)</sup>.

Furthermore, the effect of dietary fats on body fat might be determined by their source (fat-animal *v.* plant-oil source) and the specific chemical structure of the fat. Male African green monkeys received either a diet containing *cis*-MUFA or an equivalent diet containing the *trans*-isomers for 6 years<sup>(74)</sup>. *Trans*-fat fed monkeys gained significantly more weight with an increased intra-abdominal fat deposition even in the absence of energy excess. *Trans*-fat consumption was also associated with IR. On the contrary, consuming fish oil (instead of corn oil) during the 4 weeks of a high-fat dietary feeding study in rats partially protected against both the high-fat diet-induced increase in visceral fat mass and muscle IR<sup>(75)</sup>. Moreover, in rats fed a high-fat diet for 7 weeks, supplementation with marine *n*-3 fatty acids resulted in smaller visceral adipose depots and decreased plasma lipid concentrations, compared with the high-fat diet control group<sup>(76)</sup>. Interestingly, both weight gain and body composition, including body fat percent, were similar in the two feeding groups, indicating that *n*-3 fatty acid feeding led to a redistribution of fat away from the visceral compartment rather than to a reduction in total fat volume. Olive oil, especially extra virgin olive oil, was also demonstrated to improve body composition, to diminish the accumulation of VAT mass and to improve the lipid profile in high-fat diet-fed rats<sup>(77)</sup>.

#### Atherosclerosis and cardiovascular health

Atherosclerosis is a chronic inflammatory process affecting the entire arterial system that may lead to severe clinical manifestations and death. It often starts in childhood and progresses gradually in a cumulative fashion, remaining asymptomatic for decades<sup>(78)</sup>. It is a complex process of biochemical and cellular events occurring within the arterial wall, involving multiple cell types, interactions of many different molecular pathways and a variety of circulating mediators. Atherosclerotic lesion formation and progression depends on genetic make-up, sex and certain well-recognised risk factors, such as smoking, obesity, diabetes and deranged lipid profiles<sup>(79)</sup>.

Dietary interventions and specific dietary items have a substantial influence on body fat distribution and subsequently on metabolic dysfunction, but do they affect cardiovascular morbidity? The MELANY<sup>(80)</sup> is a prospective study of the Israel Defense Forces Medical Corps, in which 37 674 apparently healthy young men whose BMI was measured at adolescence were followed into early adulthood. We reported that an elevated BMI in adolescence, as early as the age of 17 years, and most importantly – one that is well within the range, currently defined as normal, has distinctive relationships with type 2 diabetes and CHD later in life. Diabetes was influenced mainly by recent BMI and weight gain, *i.e.* shortly before diagnosis, whereas for CHD both elevated BMI in adolescence and recent BMI were independent risk factors. Furthermore, two TAG measurements obtained 5 years apart in the MELANY could assist in assessing CHD<sup>(81)</sup> risk in young men, suggesting that a decrease in initially elevated TAG levels is

associated with a decrease in CHD risk compared with stable high TAG levels, while this risk remains higher than in those with persistently low TAG levels. These findings indicate that the natural history of CHD (in contrast with that of diabetes) is probably the consequence of cumulative atherosclerosis during adolescence and early adulthood that leads to clinically important disease in midlife.

The DIRECT<sup>(82)</sup>, a 2-year Israeli dietary intervention study that examined the metabolic effects of Mediterranean, low-CHO and low-fat diets, demonstrated a differential effect of the various diets on changes in lipid and glycaemic biomarkers known to be associated with cardiovascular risk. The results suggest that the dietary composition modifies these cardio-metabolic biomarkers independently of weight loss. It appears that these effects are mediated, at least partially, by the specific diet components. At the 4-year DIRECT follow-up study<sup>(83)</sup>, after the 2-year intervention was completed, there were persistent and significant reductions from baseline in TAG and total cholesterol levels, and in the LDL:HDL-cholesterol ratio, especially in the Mediterranean and low-CHO diet groups. Hence, a 2-year intervention trial, involving healthy dietary changes, demonstrated 6-year long-lasting, favourable post-intervention effects, despite a partial regain of weight during the follow-up period.

The Spanish PREDIMED trial<sup>(84)</sup> compared two energy-unrestricted Mediterranean diets, one supplemented with extra-virgin olive oil and the other with nuts, with a control low-fat diet among high-risk persons. This trial demonstrated that in both Mediterranean diet groups, the incidence of major cardiovascular events was substantially reduced. Interestingly, as all the interventions were intended to improve the overall dietary pattern, the major between-group differences involved the supplemental items. Thus, extra-virgin olive oil and nuts were probably responsible for most of the observed benefits of the Mediterranean diets.

Several studies suggest that dietary interventions can halt the progression of atherosclerosis<sup>(85–88)</sup>. In the DIRECT trial, all three dietary strategies were found to be effective in diminishing the carotid artery intima–media thickness and carotid vessel wall volume as determined by three-dimensional ultrasound. These carotid wall changes appeared to be mediated mainly by the weight loss-induced reduction in systolic blood pressure. This effect was more pronounced among mildly obese subjects who lost >5.5 kg body weight and whose systolic blood pressure declined by >7 mmHg during the intervention.

The beneficial effects of healthier dietary habits are beyond simple weight loss, as we have demonstrated recently<sup>(89)</sup>. Two patterns of adipokine and other biomarker dynamics were elucidated; whereas one pattern closely reflects weight changes, the other is suggestive of cumulative beneficial effects, possibly reflecting a delayed response to the initial weight loss or perhaps to sustained healthful dieting. Thus, weight reduction is not the sole indicator of the beneficial effects of healthful dieting, and the measurement of specific biomarkers may provide important information even in those with partial weight maintenance/regain.

Several studies addressed the effects of diet on fat depots and consequently on atherosclerosis and/or cardiovascular health. A study on diabetic pigs has suggested that a high-saturated fat/cholesterol diet induces more inflammation, atherosclerosis and ectopic fat deposition compared with an isoenergetic high-unsaturated fat diet<sup>(90)</sup>. In humans, a high-protein diet was associated with a greater decrease in adipocyte diameter and improvement in cardiometabolic risk factors<sup>(91)</sup>. A 12-week dietary randomised study reported that a reduction of 26.6% in fat mass was associated with an improvement of the cardiovascular risk profile in overweight individuals with contemporarily treated coronary artery disease<sup>(92)</sup>. Finally, a recent review<sup>(93)</sup> noted that the Mediterranean diet is beneficial in reducing the combination of heart disease and obesity in the general population as a primary care intervention.

### Summary and Conclusions

Visceral obesity and atherosclerosis should be approached as modifiable rather than ineluctable conditions. Different life-style and dietary strategies were developed to diminish these morbid processes and their impact on health. Moreover, specific foods and food components emerge as having significant effects, both beneficial and adverse, on accumulation of the morbid tissues and hence on health outcomes. For example, the type of the lipid provided in diets appears to be more important than its quantity, especially when considering body fat accumulation and distribution, and metabolic influences.

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