Ectopic fat: the true culprit linking obesity and cardiovascular disease?

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Summary

Obesity is a major risk factor for cardiovascular disease and its complications. However, not all fat depots share the same characteristics. Recent studies have found that ectopic rather than subcutaneous fat accumulation is associated with increased cardiometabolic risk. However, ectopic fat accumulation can be seen initially as a protective mechanism against lipotoxicity. Subsequently the adipose tissue becomes dysfunctional, thus inducing systemic metabolic alterations (through release of cytokines) or specific organ dysfunctions. The purpose of this review is to summarise the current available data on the impact of excess adiposity vs ectopic fat in the development of cardiometabolic diseases.

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Introduction

It is recognised that obesity is a major risk factor for cardiovascular disease (CVD), in particular coronary heart disease (CHD) and stroke, but also for systemic hypertension, metabolic dyslipidaemia, inflammation, and thrombosis (1–4). These results prompted the American Heart Association to consider obesity as a major CVD risk factor in 1998 (5). Furthermore, obesity has been shown to be associated with the development of type 2 diabetes (T2DM), with excess adiposity being a key contributor to the development of insulin resistance through the increased release of free fatty acids (FFA) and the development of lipotoxicity (6–8). With the advance of imaging techniques it has been shown that ectopic fat can accumulate in organs such as liver, heart, muscle and pancreas impairing organ function, and also releasing factors that can increase cardiovascular risk (8, 9). Thus, it has been suggested that not general obesity per se but ectopic fat accumulation was responsible for increased cardiometabolic risk.

In the following paragraphs we have reviewed the current available data to understand the impact of excess adiposity vs ectopic fat in the development of CVD.

Sites of adipose tissue accumulation

Adipose tissue accumulates predominantly as subcutaneous (SC), visceral fat (VF) and intrathoracic fat (10–12). SC forms a fat layer under the skin, the visceral adipose tissue surrounds inner organs in the abdominal cavity while the intrathoracic fat is accumulating around the heart as epicardial or mediastinal fat (10, 11). Moreover, ectopic fat can accumulate inside organs as liver, heart, pancreas and muscle, altering their metabolic activity (9, 11, 12). Many studies have shown that it is not the total amount of fat but rather its distribution that increases the risk of CVD and that excess abdominal fat (measured as increased waist circumference, WC) is a CVD risk factor stronger than body mass index (BMI) (13–30). This also explains, at least in part, why men, that are more prone to accumulate abdominal fat, are at higher risk than women to develop CVD. This observation was initially made by G. B. Morgagni who observed more than 250 years ago, during an autopsy, the accumulation of fat as visceral and mediastinal adipose tissue, and described the association between visceral obesity, hypertension, hyperuricaemia, atherosclerosis and obstructive sleep apnea syndrome, long before the modern recognition of the metabolic syndrome (31). Several years later, in 1947, a French physician, Jean Vague, reported that his obese patients with diabetes and clinical signs of CVD had a central distribution of body fat (referred as male-type or android obesity), whereas he suggested that the typical female body fat pattern of lower fat accumulation (he introduced the term “gynoid” obesity) was rarely associated with complications and more frequently found in premenopausal women (31, 32). He concluded that the common complications of obesity, such as insulin resistance, atherogenic dyslipidaemia, T2DM, and CVD, were more closely related to the distribution of body fat than to the absolute degree of fatness per se.

Since then, the advance in imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) have increased the ability to precisely and reliably quantify individual differences in body fat distribution. Using these techniques, the substantial variation in regional fat accumulation at any BMI has been documented, showing that the ability to store fat in various adipose tissue compartments could markedly differ from one individual to another (33). Moreover, using MR spectroscopy (MRS) it has been shown that fat can also accumulate in ectopic...
sites such as liver, pancreas and heart (Figure 1) causing lipotoxicity and derangement in organ metabolism possibly increasing cardiometabolic risk (8).

The metabolically healthy obese (MHO) vs normal weight but metabolically obese subjects (NWMO)

The adipose tissue is now recognised as an endocrine organ with an important role in the regulation of glucose metabolism, lipolysis and free fatty acids (FFA) release in the peripheral circulation and also as a source of pro- and anti-inflammatory markers. However, it is only when the adipose tissue becomes dysfunctional that obesity is associated with the development of disease.

Not all obese subjects are at risk of cardiometabolic disease and not all lean subjects are free of risk. Two particular phenotypes are representative of this phenomenon: the metabolically healthy obese subjects (MHO) and the subjects with normal weight but metabolically obese (NWMO). Several studies reported data on metabolically ‘healthy’ obese (MHO) individuals that seem to be protected against metabolic and cardiovascular obesity comorbidities and often display absence of dyslipidaemia, hypertension, T2DM and lower intima media thickness of the carotid artery than the majority of metabolically ‘unhealthy’ obese patients (34-37).

It has been estimated that over 30% of obese patients are metabolically healthy, have normal insulin sensitivity and do not show any criterion of metabolic syndrome, according to the IDF criteria, excluding waist circumference (34, 38). Data from the RISC study have shown that even when free from metabolic syndrome and with normal glucose tolerance, overweight/obese subjects have a less favourable cardiometabolic profile, characterised by a higher total and low-density lipoprotein (LDL)-cholesterol value, lower high-density lipoprotein (HDL), increased values of high-sensitivity C-reactive protein (CRP) and blood pressure, as well as thicker intima media of common carotid segment. This suggests a potentially susceptibility to CVD (38). However, in long-term prospective studies (7-15 years) MHO were not found at increased risk of CVD and all-cause mortality (39, 40). It has not been clarified whether healthy obese individuals can maintain insulin sensitivity during the entire life or whether healthy obesity simply represents delayed onset of obesity related insulin resistance (41).

Several normal weight individuals are characterised by hyperinsulinaemia, hyperglycaemia, insulin resistance (IR), impaired glucose tolerance (IGT), hypercholesterolaemia and hypertriglyceridaemia, and are therefore ‘metabolically obese’ (NWMO) (42). These characteristics in lean individuals mark a departure from common human patterns in which metabolic disease is a consequence of weight gain. These phenotypes are very prevalent. The analysis of the Framingham study have shown that over 40% of men and women had increased VF, despite an average BMI of 27 kg/m² in women and 28 kg/m² in men (43). Metabolic abnormalities can be observed also in non-obese subjects with ectopic fat accumulation, such as non-alcoholic fatty liver disease (NAFLD), characterised by hepatic steatosis (44) or in lean women with polycystic ovary syndrome (PCOS) (45). Elevated risk for CVD is common in subjects NWMO (46), as well as elevated risk for hypertension, T2DM and other metabolic complications and it has been recently reported that normal weight adults at the time of diagnosis of diabetes have higher cardiovascular and non-cardiovascular mortality than adults who were overweight or obese (47).

When the “adipose organ” becomes dysfunctional

The adipose tissue is a dynamic organ where new adipocytes are formed and old adipocytes change in size and metabolism. It is only when the adipose tissue becomes dysfunctional, with infiltration of chronic inflammatory cells like macrophage and lymphocytes that it releases inflammatory factors and shows alteration in lipid metabolism, contributing to the development of insulin resistance, endothelial dysfunction and in general to the increase in cardiometabolic risk.

Failure to make new adipocytes and enlarged adipocyte size is considered a marker of adipocyte dysfunction (48). Human studies of adipose tissue morphology have shown that we have an average of between 20 to 40 billion mature adipocytes but this number can be doubled or even tripled in massively obese patients depending upon their adipose tissue mass (49-51). Human adipocytes can grow up to ~20 fold in diameter and several thousand-fold in volume (52). Studies that have examined the relationship between adipose cell size and number have generally reported that large subcutaneous fat cells are associated with metabolic derangements possibly due to hypoxia whereas adipose cell number does not appear, per se, to be detrimental to cardiometabolic health in the presence of normal size adipocytes (53). In non obese subjects lower insulin sensitivity is correlated with large abdominal adipocytes, increased adipokine release and lower GLUT-4 expression (54).

Initially, it was believed that subcutaneous fat cells themselves could contribute to the dysmetabolic state of obesity until it was found that excess visceral fat is more closely related to metabolic complications than subcutaneous fat cell size. It has been hypothesised that excess visceral adiposity may rather be a marker of the relative inability of the SC to expand through hyperplasia in the face of a positive energy balance (29) an hypothesis recently confirmed in a work studying the effect of overfeeding (55). Alligier et al. have shown that not all subjects increase VF after overfeeding but only those with a defective gene expression in the regulation of lipid-storing genes in SC (55). Although ectopic fat accumulation was not measured in this study, this supports the hypothesis that in presence of lipid overflow and impairment in SC tissue to store it, this accumulates in other tissues. Under conditions of fat overflow (56) SC tissue would enlarge adipocytes, that would secrete pro-inflammatory adipokines (e.g. tumour necrosis factor [TNF]-α, interleukin [IL]-6, and IL-1), reduce secretion of anti-inflammatory and insulin sensitising cytokine, e.g. adiponectin, and would become prone to apoptosis (57-59). As a consequence, such hypertrophic adipose depots may become invaded by macrophages, and
a vicious cycle would develop with a harmful cross-talk of deleterious secretory products between the macrophages and the enlarged fat cells (57-59).

Recently it has been shown that adipose tissue, in particular VF, can produce significant amount of plasminogen activator inhibitor 1 (PAI-1), a peptide involved in fibrinolysis and plaque formation and a risk marker of atherothrombosis and ischaemic heart disease. PAI-1 is regulated by TNF-α, but also hyperinsulinaemia and hyperlipidaemia seem to increase its secretion (60). This is in agreement with studies showing that obese subjects, especially those with preferential abdominal fat accumulation and with NAFLD, have increased plasma levels of PAI-1 (61) and that decrease in VF, but not SC, after weight loss was correlated with lower PAI-1 levels (60).

Some of the adipokines, like TNF-α and IL-6, impair adipocyte differentiation, reduce lipid accumulation, and increase adipocyte lipolysis others interfere with insulin signalling. Hypertrophic adipocytes are not only stressed, but also display reduced ability to take up and release FFA. This induces a redirection of lipids towards peripheral tissues, including skeletal muscle, liver, pancreas, and heart, causing ectopic fat deposition (Figure 1). If in these tissues, lipid supply exceeds oxidative capacity intracellular lipid accumulation occurs, causing lipotoxicity and impairment in organ function (Figure 1). Moreover, increased inflammation, adipokine release, high FFA, hyperinsulinaemia and hyperlipidaemia are involved in the development of metabolic syndrome and increased cardiometabolic risk (Figure 2).

**Ectopic fat and CVD**

A key unanswered question is the respective contribution of the various ectopic fat depots, including the expanded visceral adipose tissue, to cardiometabolic risk. It is well established that ectopic fat accumulation is not preferentially located in one organ but it is often found simultaneously in several organs, among which liver, heart, muscle and pancreas (12, 62, 63). Ectopic fat in muscle and pancreas are possibly related to peripheral insulin resistance and...
Epicardial and intra-myocardial fat and CVD

Around 80% of the heart is surrounded by epicardial fat which accounts 20% of total heart weight (11, 64, 65). If epicardial fat is contributing to increase cardiometabolic risk is still controversial (66). Several cross-sectional studies have suggested a positive relationship between increased epicardial fat volume and coronary artery disease (CAD) (67-70), myocardial infarction (71), systemic inflammation (72), reduced cardiac energy metabolism (73), insulin resistance in obese non-diabetic patients (74) and in Chinese T2DM subjects (75, 76). In the studies where epicardial fat was found associated with CVD also mediastinal fat was associated with CVD (66), and the increase in epicardial fat is mirrored by the increase in mediastinal as well as total fat (11, 65).

As demonstrated in animal models, epicardial fat might protect the myocardium from high circulating fatty acid levels providing fatty acids as a direct energy source (11, 77, 78). Moreover, epicardial fat might have a mechanic function by surrounding coronary arteries and reducing artery shear stress (11). Epicardial fat compartment could act as a metabolically active organ by secreting cytokines (72), so it is possible that only when in subjects where it has become dysfunctional it is associated with cardiometabolic risk, as in patients with established disease (11). However, imaging studies can only measure the size of fat accumulation and not the metabolic status.

Different is the ectopic fat accumulated inside cardiomyocytes as intramyocardial triglyceride, IM-TG (66). Patients with IGT and T2DM have increased myocardial TG content compared to obese and lean controls (79-81), showing that insulin resistance can favour intramyocardial fat accumulation. In fasting conditions, cardiac metabolism relies mainly on fatty acid uptake and oxidation. Thus, in the presence of excess circulating FFA, mainly because of insulin resistance, it is plausible to hypothesise an increased uptake of cardiac FFA that are then re-esterified to triglyceride instead of being oxidised (66). High rate conversion of fatty acids in myocardial TG is associated with intermediates (e.g. ceramide) release which is associated with mitochondrial dysfunction and impaired cardiac function in animal models (82, 83). In T2DM patients, increased TG myocardial content was associated with impaired left ventricular diastolic function (83) (▶Figure 2).

Hepatic fat and CVD

Subjects with NAFLD have an increased cardiometabolic risk (84-86). The real prevalence of CV events in patients with NAFLD is still not known and probably underestimated. NAFLD is often not diagnosed since in the great majority of NAFLD subjects hepatic enzymes are within normal range and ultrasound technique is unable to detect NAFLD when fat infiltration is below 30% (87, 88). In general the cardiometabolic risk is increased in subjects with NAFLD, even if they do not have the metabolic syndrome and are at low risk for CVD (86). If hepatic fat plays a direct role in the development of CVD is, however, still controversial.

Some factors that can explain the increased CVD risk in subjects with NAFLD are the increased lipolysis and VLDL secretion (44, 89), the atherogenic lipoprotein profile (19), but also hyperglycaemia due to hepatic overproduction of glucose. Fat accumulation in the liver and oxidative stress induce the secretion of inflammatory markers such as fibrinogen and CRP, insulin-like growth factor (IGF)-1, TNF-α, fetuin-A, (44, 90, 91). All these metabolic abnormalities, common in subjects with NAFLD, have been shown to directly or indirectly promote atherosclerosis as confirmed by studies that showed increased intima media thickness (IMT) and coronary atherosclerosis (85, 86, 90, 92, 93). NAFLD has been found also associated with endothelial dysfunction and CAD (86, 92, 94-96).

Visceral fat and CVD

An excess of intra-abdominal or VF has been reported to be associated with a constellation of metabolic abnormalities including insulin resistance, hypertension, hyperinsulinaemia, glucose intolerance, T2DM, atherogenic high triglyceride. Moreover, subjects with VF have increased serum concentration of small dense LDL, low HDL, dyslipidaemia, inflammation, altered cytokine profile, impaired fibrinolysis, and increased risk of thrombosis, and endothelial dysfunction (29, 97-106). In patients with T2DM, plasma lipoprotein levels (107) and inflammatory markers (108) are strictly correlated with visceral adiposity that was independent from metabolic control. In addition, VF accumulation has been correlated with hepatic and cardiac fat and similarly predicted metabolic and cardiovascular alterations (65, 70, 91, 106, 109). Recent large cohort studies such as the Framingham Heart Study and the Jackson Heart Study that have extensively used CT, have shown that excess visceral adiposity (along with other markers of excess ectopic fat deposition such as increased cardiac, hepatic and intrathoracic fat) is significantly correlated with various cardiometabolic abnormalities in a manner that is independent of the amount of subcutaneous fat (70, 109-114). However, these results should be interpreted with caution, since none of these studies was designed to answer this question and correlations do not prove causation. Moreover, none of the above described abnormalities (e.g. insulin resistance, hyperlipidaemia, increased risk of thrombosis, endothelial dysfunction) can be directly related to excess VF. On the other hand VF could secrete adipokines that can impair the metabolic signalling, at least in part contribute to hyperlipidaemia through hepatic lipid overflow and explaining its association with increased CVD risk (62).
Ectopic fat reduction: a therapeutical target?

Reducing CVD risk by weight loss and/or increasing energy expenditure is still a matter of discussion. Despite the variety of weight loss methods, it remains unclear whether relative rates of change in ectopic fat and/or VF can be specifically manipulated and in the long term.

Lifestyle intervention: caloric restriction

Caloric restriction, as low (LCD) or very low caloric diet (VLCD, < 800 kcal/day), is effective in decreasing both total and ectopic fat and in improving cardiometabolic profile (115) (Figure 2B). All ectopic fat depots have been shown to be decreased with weight loss. In particular hepatic and visceral fat have been shown to decrease more in the early weeks of diet and percent weight loss was inversely associated to the relative ratio of percent changes in VF vs SC fat (115). Weight loss was also associated with decrease in hepatic fat and both changes in visceral and hepatic fat correlated with the improvement in peripheral and hepatic insulin resistance (116). However, subjects with high VF and high hepatic fat have a lower chance of profiting from lifestyle intervention and may require intensified lifestyle prevention strategies or even pharmacological approaches to improve insulin sensitivity (117). Diet-induced weight loss was associated with a significant decrease in epicardial fat thickness measured over the right ventricle wall by echocardiography (11, 12, 118). Moreover, the change in diastolic function was also positively correlated with the change in epicar-
dial fat thickness (118). The effects of diet on pericardial fat and other TG stores in obese T2DM patients treated for 16 weeks with VLCD followed by 14 months of a regular diet were evaluated by MR imaging and spectroscopy. Loss of VF and epicardial fat was more pronounced as compared to SC during the intervention study, but VF was in part regained during 14 months follow-up period. Surprisingly, epicardial fat was the only fat compartment that did not expand during the additional 14 months follow-up (119). Weight loss was also associated to a decrease in intramyocardial TG. Obese patients with TZD following for 16 weeks a VLCD (450 kcal/day) had a significant decrease in BMI (from 35.6 ± 1.2 to 27.5 ± 1.3 kg/m²) associated with a significant decrease in myocardial TG content (from 0.88 ± 0.12% to 0.64 ± 0.14%) and an improvement in left ventricular diastolic function (120).

Several studies have shown that weight loss decreases hepatic TG content in obese and T2DM subjects (64, 117, 121, 122). Studies measuring both hepatic TG content and hepatic insulin sensitivity with a hyperinsulinaemic euglycaemic clamp in obese NGT and T2DM patients, found an improvement in hepatic insulin sensitivity that was associated with the decrease in intrahepatic lipids (117, 122).

**Lifestyle intervention: physical exercise**

The effects of exercise per se on ectopic fat volume and distribution are still not well established. After a six-week aerobic exercise program (60–85% of VO₂max for a minimum of 20 minutes [min] at least three times per week) (125), although no significant effects on body weight and hepatic TG content as measured by 1H-MRS were found, both peripheral and hepatic insulin sensitivity (measured by the hyperinsulinaemic euglycaemic clamp) improved (123). On the contrary, in obese NGT subjects, a one-month aerobic exercise training (3 times/week, 3–45/min at max 70%VO₂max) decreased hepatic TG concentration by 21% (123). In general if exercise was not accompanied by weight loss there was little decrease in liver fat but no improvement in liver metabolism (124).

In a three-month exercise program in obese NGT middle-aged Japanese men, BMI decreased by 4.3 ± 3.0% (circa −1 kg/m²) and VO₂max increased by 20% leading to a change in visceral adipose tissue (~15%) that was significantly correlated with the change in epicardial adipose tissue (~8.6%) (125). This findings were confirmed in a trial in which 32 obese postmenopausal women were randomised to diet-only or diet combined with moderate or intensive exercise for 20 weeks. The three groups had similar reduction in bodyweight (~15%) and pericardial fat (~17%) that were not affected by the type of intervention (100).

**Bariatric surgery**

Bariatric surgery (BS) has been demonstrated to induce important weight loss in obese patients and to reduce cardiovascular mortality and cardiovascular events by 50% in patients with severe obesity (126, 127). BS is associated with decrease in all fat depots and a drastic reduction in biological cardiovascular risk markers, such as inflammatory and insulin resistance parameters (128, 129) (▶ Figure 2). BS is also associated with remission of diabetes, decreased CVD risk factors and mortality rate (127, 130-132). It has been reported that on average, hypertension remitted or resolved in 68%, diabetes in 75%, and dyslipidemia in 71% after BS (130-132).

The amount of fat lost with bariatric surgery during a fixed time frame is greater with Roux and Y gastric bypass (RYGB) and biliopancreatic diversion (BPD) compared to Laparoscopic Gastric Banding (LAGB) and sleeve gastrectomy (SG) (131, 132). However, whether different surgical procedures, rather than weight loss per se, have different impact on cardiometabolic risk is still a matter of debate. Indeed, when we compared the effects of similar weight loss (i.e. 20% of initial weight) induced by LAGB or RYG we found similar improvement in insulin sensitivity, β-cell function, and oral glucose tolerance in non-diabetic obese adults (133).

Already after six months it is possible to observe an improvement in cardiac function, particularly diastolic function. In general all fat depots decreased but the reduction in epicardial fat volume (EFV) was independent of the reduction in BMI and VF, while no change was observed in intramyocardial fat (134). Similarly BS decreased also hepatic fat, often improving liver histology and resolving non-alcoholic steatohepatitis (NASH) (135). In general, BS improves the entire cardiometabolic profile with decrease in serum transaminases, γ-glutamyltransferase, glucose and insulin. The cardiometabolic improvement obtained after weight loss surgery results in significant reduction in circulating lipid concentrations with triglyceride levels consistently reduced both immediately and after long-term follow-up (130, 131). Greater improvements are observed after RYGB and BPD, (TG decreased up to 50% to 60% and HDL cholesterol increased up to 47%) in contrast to gastric procedures in which triglyceride levels are reduced by only 16% to 25% (130, 131). Moreover, the great majority of patients requiring lipid-lowering therapy preoperatively were able to discontinue hypolipidaemic drug regimens after BS (130, 131).

**Pharmacological intervention**

An important question is whether the abnormal pattern of fat distribution can be reversed and whether dysfunctional fat cells can be converted to healthy adipocytes, leading to enhanced muscle/hepatic sensitivity to insulin and improved β-cell function. Since weight loss is associated to reduction in ectopic fat, all drugs that favour weight loss are associated with a decrease in ectopic fat and have a positive effect on cardio-metabolic parameters. Among the drugs that have been shown to effectively reduce ectopic fat, thiazolidinediones (TZD) are the most effective. It has been shown that TZD reduce both visceral and hepatic fat, despite an increase in SC (8). Reduction in VF was associated also with improved glucose and lipid metabolic and reduced hyperglycaemia (136) (▶ Figure 2C). It has been observed that the greater the weight gain, the better the improvement in glycaemic control. It also is noteworthy that obese individuals respond better than lean subjects to TZD, and that women, who have a higher percentage of body fat, respond better than men (8). TZD treatment decreases...
inflammation, improves adipose tissue insulin resistance, reduce VLDL and LDL secretion and increase HDL and thus reduce most of risk factors associated with atherosclerosis and improve endothelial function (137, 138). Despite having similar effects on glycaemic control, pioglitazone and rosiglitazone appear to have different effects on cardiovascular outcomes. Rosiglitazone has been associated with an increased risk of myocardial infarction, and its use is restricted in many countries because of cardiovascular safety concerns. All TZDs increase the risk of heart failure. Moreover, pioglitazone, but not rosiglitazone, has been associated with slight reduction in liver fibrosis and hepatic inflammation (139).

Incretin-based therapies (glucagon-like peptide 1 [GLP-1], analogues and DPP-IV inhibitors) have as major effects the potentiation of insulin secretion, satiety and gastric emptying that results in improved glycaemic control. They have been also associated with various degrees of weight loss and ectopic fat reduction (140). We have recently shown that a high-fat diet induces impairment in hepatic insulin signalling and FFA oxidation and that treatment with exenatide (a GLP-1 analogue) of hepatocytes from animals with NASH improved hepatic signalling related to fat oxidation and reduced hepatic steatosis (141). Recently incretin-based therapies have been shown to have some cardiovascular protective properties. GLP-1 receptors have been found in the heart and on the endothelial wall, thus explaining the relationship between incretin therapy and reduced cardiovascular risk. Incretin analogs exert their cardioprotective action by improving cardiac function, cardiac glucose and FFA metabolism, reduce apoptosis and induce cardiac remodelling (142). Moreover, they improve endothelial function by increasing nitric oxide release and they reduce inflammation (142).

Conclusions

Ectopic fat may be assimilated to an endocrine organ able to secrete a number of active substances. Data support its role as a relevant link between risk and clinical conditions such as metabolic syndrome, diabetes, hypertension and cardiovascular diseases. Only when the adipose tissue becomes dysfunctional and mitochondrial oxidation is impaired, reactive oxygen species are produced, cytokines released and ectopic fat becomes responsible for impairment in organ metabolism and implicated in the development of CVD. However, this relationship remains to be fully elucidated in properly designed clinical trials. Imaging techniques show an accurate diagnostic yield, but their clinical use is not standardised and clinical algorithms do not envision fat assessment for risk stratification. Ectopic fat may become the target for therapeutic interventions, aimed at its reduction to counteract its dysfunctional activities. It is conceivable that ectopic fat becomes the diagnostic target in metabolic disorders shifting the focus from quantity (obesity) to quality (dysfunctional fat).

Abbreviations

FFA, free fatty acid; HGP, hepatic glucose production; VLDL, very-low-density lipoprotein; NASH, non-alcoholic steatohepatitis; NAFLD, non-alcoholic fatty liver disease; VO₂ max, maximal oxygen consumption; TNF-α, tumour necrosis factor alpha; IL-6, interleukin 6; PAI-I, plasminogen activator inhibitor 1; BMI, body mass index; IGT, impaired glucose tolerance; T2DM, type 2 diabetes mellitus; TG, triglycerides; IGF-1, insulin-like growth factor; IMT, intima media thickness; NGT, normal glucose tolerance; SC, subcutaneous fat; VF, visceral fat; BS, bariatric surgery; RYGB, Roux and Y gastric bypass; LAGB, laparoscopic gastric banding; BPD, bilio-pancreatic diversion; GLP-1, glucagon-like peptide 1.

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Conflicts of interest

None declared.

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