Visceral and ectopic fat, atherosclerosis, and cardiometabolic disease: a position statement

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Findings from epidemiological studies over the past 30 years have shown that visceral adipose tissue, accurately measured by CT or MRI, is an independent risk marker of cardiovascular and metabolic morbidity and mortality. Emerging evidence also suggests that ectopic fat deposition, including hepatic and epicardial fat, might contribute to increased atherosclerosis and cardiometabolic risk. This joint position statement from the International Atherosclerosis Society and the International Chair on Cardiometabolic Risk Working Group on Visceral Obesity summarises the evidence for visceral adiposity and ectopic fat as emerging risk factors for type 2 diabetes, atherosclerosis, and cardiovascular disease, with a focus on practical recommendations for health professionals and future directions for research and clinical practice. We discuss the measurement of visceral and ectopic fat, pathophysiology and contribution to adverse health outcomes, response to treatment, and lessons from a public health programme targeting visceral and ectopic fat. We identify knowledge gaps and note the need to develop simple, clinically applicable tools to be able to monitor changes in visceral and ectopic fat over time. Finally, we recognise the need for public health messaging to focus on visceral and ectopic fat in addition to excess bodyweight to better combat the growing epidemic of obesity worldwide.

Introduction

Since 1980, the prevalence of obesity has doubled in more than 70 countries and continues to increase worldwide.[1] In the USA alone, the age-adjusted prevalence of obesity (defined by BMI ≥30 kg/m² was estimated to be 38% (35% of men and 40% of women) in 2014, and about 8% had class III obesity (6% of men and 10% of women), the most severe form of the disorder (defined as BMI ≥40 kg/m²).[2] However, although BMI might be a convenient and simple index to monitor the growth in obesity prevalence at the population level, studies have shown that obesity defined by BMI is remarkably heterogeneous[3] and that people with similar bodyweight or BMI values can have substantially different comorbidities and levels of health risk.[4] Moreover, although a substantial minority of individuals with obesity have no or few cardiometabolic risk factors,[5] the concept of metabolically healthy obesity is largely determined by which cutoffs are used to define abnormal risk factors.[6] Furthermore, studies have shown that almost half of adults with so-called metabolically healthy obesity will develop metabolic syndrome and have higher odds for future cardiovascular disease.[7] Even though the limitations of BMI as an index of obesity have been known for decades, and newer, more specific measures of adiposity-related risk have been developed, many obesity guidelines[8–12] continue to recommend BMI as the optimal tool to measure obesity-related morbidity and mortality risk.

The inability of BMI to fully capture cardiometabolic risk is partly related to the fact that BMI in isolation is an insufficient biomarker of total body, and, more importantly, central abdominal fat mass and does not account for the extreme variation in intra-abdominal (visceral) fat distribution between individuals.[13] For example, figure 1 shows T1-weighted MRI coronal abdominal images in two individuals, one near-normal bodyweight (BMI 25 kg/m²) and one with obesity (BMI 30 kg/m²). Here, BMI misrepresents the burden of visceral adipose tissue (VAT) between the two individuals. Several large cardiometabolic imaging studies, using CT or MRI, have shown that abdominal fat depots are heterogeneous and differentially associated with atherosclerosis and cardiometabolic risk.[14,15] Data from several epidemiological studies over the past 30 years have shown that VAT is an independent marker of morbidity and mortality, and abdominal subcutaneous adipose tissue (SAT) accumulation is a much weaker indicator of cardiovascular risk.[16] Emerging evidence also suggests that ectopic fat deposition, including hepatic and epicardial fat linked with increased VAT deposition, might also contribute to increased atherosclerosis and cardiometabolic risk.[17]

On April 24, 2017, the International Atherosclerosis Society and International Chair on Cardiometabolic Risk Working Group on Visceral Obesity convened in Prague, Czech Republic, to discuss the importance of visceral adiposity and ectopic fat as an emerging risk factor for premature atherosclerosis and cardiovascular disease. The group agreed to work on the development of consensus documents, which would reflect the position of the two organisations. In this position statement, we summarise the evidence for visceral adiposity and ectopic fat as emerging risk factors for type 2 diabetes, atherosclerosis, and cardiovascular disease, with a focus on practical recommendations for health professionals and future directions for research and clinical practice.

Measurement of visceral and ectopic fat

The development of medical imaging has been a remarkable advance that has revolutionised the study of human
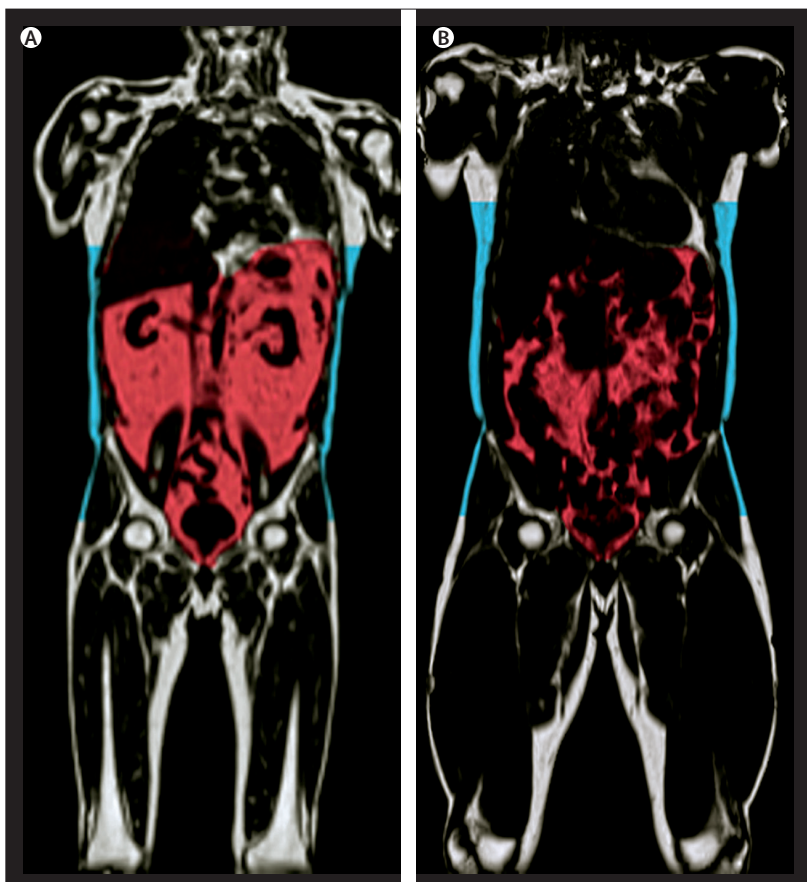
Figure 1: Variation in abdominal fat distribution
T1-weighted coronal neck-to-knee magnetic resonance images showing variation in visceral fat (red) and abdominal subcutaneous fat (blue). (A) A 67-year-old man with near-normal weight, BMI 25 kg/m², and visceral fat 2·58 L/m². (B) A 53-year-old man with obesity, BMI 30 kg/m², and visceral fat 0·88 L/m². Images from AMRA Medical (Linköping, Sweden), reproduced from Neeland and colleagues,[13] by permission of Lippincott Williams & Wilkins.

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body composition, including visceral fat.[18–20] Cross-sectional images of the body derived by CT or MRI can be generated at any level and on the basis of differences in imaging parameters of body fat, muscles, and bones, precise measurements of total and regional body composition are possible. Apart from quantifying adipose tissue depots, CT and MRI have been used to measure the quality of lean (skeletal muscle)[21] and adipose tissues.[22] Furthermore, techniques with improved spatial resolution have enabled detection and measurement of fat in areas of the body where fat is not physiologically stored, such as the liver, pancreas, heart, and skeletal muscle[13]—termed ectopic fat depots. With the availability of imaging techniques, exploration of the association between these ectopic fat depots and cardiometabolic risk factors and outcomes has been possible.[23,24] These methods have allowed investigators to identify the clinical importance of lipid accumulation in several tissues, including liver, skeletal muscle, and adipose tissue.[25] Advances in dual-energy x-ray absorp-tiometry (DEXA) suggest that this method provides acceptable estimates of total and abdominal fat distribution,

including visceral fat. The DEXA method for measuring visceral fat has been validated against direct measures using CT[26] and MRI[27] (with R^2 ranging between 0·82 and 0·96). However, unlike CT or MRI, DEXA estimates VAT on the basis of the difference between total and subcutaneous abdominal fat rather than measuring it directly. Furthermore, DEXA might slightly underestimate VAT among normal-weight individuals and overestimate it among those with very severe obesity.[27] Nevertheless, access to DEXA presents a feasible alternative to CT or MRI for quantifying visceral fat and practitioners are encouraged to consider this option to help to characterise the high-risk obesity phenotype.

Since routine access to CT, MRI, or DEXA might not be feasible for many clinicians and the use of these modalities for imaging of visceral and ectopic fat has historically been reserved for research purposes, several surrogate anthropometric indices (whether in isolation or combined with simple laboratory tests) of visceral fat have been developed (table). Perhaps the most widely used and accepted of these measurements is waist circumference. Ashwell and colleagues[35] were the first to show a correlation between the amount of visceral fat and the waist-to-hip ratio. However, compared with the waist-to-hip ratio, waist circumference alone was shown to be more strongly associated with the amount of visceral fat.[36] In a large international CT imaging study (INSPIRE ME IAA), an increased waist circumference within each unit of BMI was predictive of an increased amount of VAT.[37] In view of the frequent coexistence of excess visceral and liver fat, the combined presence of an increased waist circumference and increased triglyceride levels has been associated with a high probability (around 80%) of increased VAT levels.[33] These findings have been confirmed in other studies examining the so-called hypertriglyceridemic waist phenotype as a simple tool to screen for the presence of excess VAT and ectopic fat.[34]

VAT is not a routine measure in clinical settings. Therefore, the extent to which an increased VAT could affect the waist circumference threshold for increased cardiometabolic risk, and whether reductions in waist circumference are associated with corresponding reductions in VAT, are important issues. In the USA, many clinicians and researchers have accepted a single threshold for adults (102 cm in men and 88 cm in women) to denote a high waist circumference, irrespective of BMI.[38] However, different ethnicity-specific cutoff values for waist circumference (used in the diagnosis of the metabolic syndrome) have been proposed by the International Diabetes Federation (eg, 94 cm for European men and 80 cm for European women, and 85 cm for Japanese men and 90 cm for Japanese women).[39] Although evidence including meta-analyses suggests an association between reductions in waist circumference and VAT,[40–42] the variance explained is fairly small (about 40%).[43–45] However, to our knowledge there is no study reporting that a reduction in waist circumference is not associated with a corresponding

	Correlation with VAT	Advantages	Disadvantages
BMI	0·67–0·84[28,29]	Simple to use in the clinic; well documented in the medical literature	Fairly low correlation with VAT, especially among certain racial or ethnic groups
Waist circumference	0·50–0·87[28–31]	Simple to use in the clinic; well documented in the medical literature	No consensus on method of measurement; variability depending on location of measurement
Waist-to-height ratio (index of central obesity)	0·52–0·81[28,30]	Simple to use in the clinic; well documented in the medical literature	Does not significantly improve assessment of visceral adiposity beyond using waist circumference alone
Waist-to-hip ratio	0·67–0·71[29]	Simple to use in the clinic; well documented in the medical literature	Does not significantly improve assessment of visceral adiposity beyond using waist circumference alone
Neck circumference	0·63–0·82[31,32]	Simple to use in the clinic	Not very well documented in the medical literature
Sagittal abdominal diameter*	0·80–0·87[29]	Similar correlation with VAT as waist circumference; associated with cardiometabolic risk markers; can also be measured with CT	Difficult to implement in clinic
Hypertriglyceridemic waist†	NA‡	Integrated index including evidence of metabolic dysfunction	Additional laboratory measurement required

Data are Pearson's *R*. VAT=visceral adipose tissue. *Sagittal abdominal diameter is defined as the abdominal height measured as a line extending from skin to skin through the centre of the abdomen in the anterior–posterior direction. †Hypertriglyceridemic waist is defined by the presence of increased waist circumference (≥90 cm in men and ≥85 cm in women) accompanied by hypertriglyceridemia (≥2 mmol/L in men and ≥1·5 mmol/L in women). ‡Diagnosis of hypertriglyceridemic waist is binary (presence or absence), so the diagnosis cannot be used as a continuous variable to compute its correlation with VAT; however, hypertriglyceridemic waist is associated with a 75–85% probability of increased levels of VAT.[33,34]

Table: Non-imaging clinical methods for the assessment of visceral adiposity

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reduction in VAT. Thus, although it is reasonable to suggest that a reduction in waist circumference is associated with a reduction in VAT, precise estimation of individual VAT reduction from waist circumference is not possible. Nonetheless, the corresponding reduction of VAT with waist circumference in a dose-dependent manner highlights the importance of routine measurement of waist circumference in clinical practice. Although no consensus exists regarding the best protocol for the measurement of waist circumference, many experts have recommended measurement at the level of the iliac crest, or at the midpoint between the last rib and the iliac crest.[46]

Abdominal SAT and VAT: contribution to health outcomes

The ability to distinguish previously externally undetectable inner body-fat compartments from the SAT that is externally visible affords investigators the opportunity to quantify the relations between various body fat depots and health outcomes. Early imaging work done in the 1980s revealed that the amount of intra-abdominal adipose tissue or VAT seemed to be the strongest adipose correlate of metabolic abnormalities that had been previously attributed to an excess amount of total body fat.[47–49] There was, however, an initial confusion in the interpretation of these early data, which largely arose from a report showing that the respective correlations between SAT and VAT and metabolic outcomes were not substantially different,[50] leading some investigators to suggest that subcutaneous fat was more important to consider than was visceral adiposity and that information on visceral adiposity would not substantially improve our ability to identify high-risk patients with overweight or obesity. This problem can be explained by the fact that, at the population level, there is a

significant correlation between the sizes of SAT and VAT.[37] However, studies that have quantified individual variation in visceral adiposity have identified a variation of two to three times in visceral adiposity at any level of total or subcutaneous adiposity.[3,16,37] These observations emphasise the physiological role of SAT as the metabolic sink for excess triglycerides, albeit with a finite expansion capacity; thus, studies in rodents and human beings[51,52] have shown that when SAT is unable to expand to accommodate overfeeding, visceral and ectopic fat deposition occurs. The hypothesis that the plasticity and expandability of SAT (or lack thereof) protects (or predisposes) individuals from visceral and ectopic fat deposition and subsequent metabolic health consequences led to the concept of a so-called personal fat threshold,[51] which, if exceeded, increases the likelihood of developing metabolic disturbances such as type 2 diabetes, even when overall BMI is in the normal or mildly overweight range.[52]

Thus, to better understand whether measurement of visceral adiposity is useful or not to discriminate health risk, whether variation in visceral adiposity is associated with differences in the metabolic profile must be assessed within given levels of subcutaneous (or total) adiposity. Studies in which such analyses have been done[14,53,54] have clearly shown that, within categories of total body or subcutaneous fat, high levels of VAT are associated with disturbances in the metabolic profile. An extensive discussion of the constellation of metabolic abnormalities associated with a selective excess of VAT is beyond the scope of this position statement, but several reviews on the topic have been published over the past 25 years.[13,17,47,55–58]

Many health and metabolic abnormalities are associated with an excess of VAT (figure 2). Type 2 diabetes is one such health consequence that might be reversed to
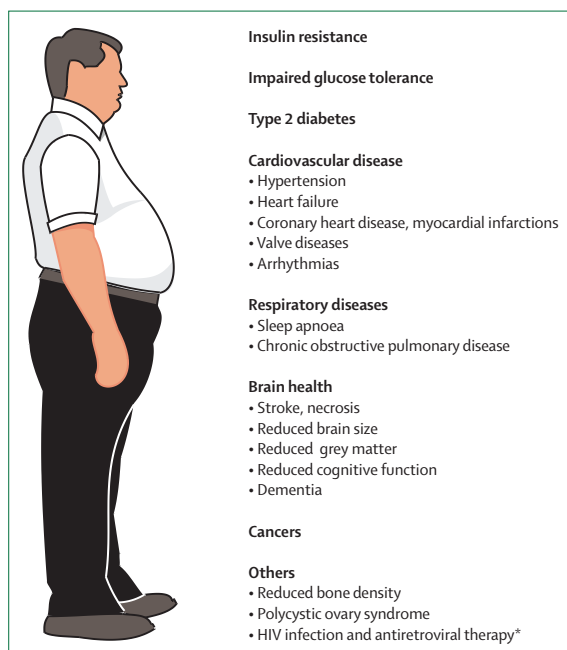
Insulin resistance

Impaired glucose tolerance

Type 2 diabetes

Cardiovascular disease
• Hypertension
• Heart failure
• Coronary heart disease, myocardial infarctions
• Valve diseases
• Arrhythmias

Respiratory diseases
• Sleep apnoea
• Chronic obstructive pulmonary disease

Brain health
• Stroke, necrosis
• Reduced brain size
• Reduced grey matter
• Reduced cognitive function
• Dementia

Cancers

Others
• Reduced bone density
• Polycystic ovary syndrome
• HIV infection and antiretroviral therapy*

Figure 2: **Health and metabolic abnormalities associated with an excess of visceral adipose tissue**
Figure shows a list of clinical outcomes that have been reported to be associated with an excessive accumulation of visceral adipose tissue and ectopic fat irrespective of total adiposity estimated by BMI. For some of these conditions, evidence for a causal relation is insufficient. *HIV infection and antiretroviral therapy can contribute to the accumulation of visceral adipose tissue and ectopic fat.

normal glucose tolerance by substantial weight or VAT loss (whether by diet, pharmacotherapy, or surgery). For example, in early type 2 diabetes, a negative calorie balance decreases liver fat and normalises regulation of hepatic gluconeogenesis.[59] Over the subsequent weeks, a continued caloric deficit improves intra-pancreatic fat levels and normalises first-phase insulin secretion.[59] Even in the long-term (up to 5 years), among people who undergo weight loss with bariatric surgery, BMI is lowered by 20%, and 23–29% of patients are able to achieve an HbA$_{1c}$ level of 6·0% (42·1 mmol/mol) or less with or without diabetes medications, compared with 5% among those treated with intensive medical therapy alone.[60] Notably, even among individuals without obesity, targeted fat reduction can improve glycaemic control; this observation is consistent with the concept of the personal fat threshold.[52]

Pathophysiology of visceral and ectopic fat

Growing evidence suggests that VAT is a key conduit through which obesity predicts health risk. Visceral adiposity can be described as a consequence of a pathological response of SAT to positive caloric balance (inability of SAT to expand through hyperplasia of preadipocytes) in susceptible individuals, contributing directly and indirectly to cardiovascular and metabolic diseases. Excess visceral adiposity is characterised by increased visceral and ectopic fat deposition, adipocyte dysfunction, inflammatory and adipokine dysregulation, and insulin resistance. Multiple factors might influence fat deposition in various depots, including age, sex, race or ethnic origin, genetics and gene expression, the potential for adipose tissue expansion (hyperplasia vs hypertrophy), and response to weight gain.[3,13]

The mechanisms by which an excess of VAT is related to various health outcomes are not fully understood and are under investigation. Several comprehensive reviews have been published on the topic[3,55,61] and only a brief summary is provided here. Three non-mutually exclusive scenarios have been proposed to explain the cardio-metabolic complications found among individuals with an excess of VAT: first, that VAT has metabolic properties that are distinct from SAT; second, that excess VAT induces inflammation; and third, that VAT is a marker of increased ectopic fat.

VAT and SAT have distinct metabolic properties

Because most VAT is drained by the portal vein, the hyperlipolytic state of large (hypertrophic) adipocytes associated with visceral obesity exposes the liver to high concentrations of free fatty acids and glycerol, leading to several impairments in liver metabolism, such as reduced hepatic extraction of insulin (exacerbating hyper-insulinemia), and increased production of triglyceride-rich lipoproteins, as well as increased production of hepatic glucose, which explains the link between visceral obesity and glucose intolerance and type 2 diabetes.[62] Free fatty acids have been shown to serve as ligands for peroxisome proliferator-activated receptor-α and hepatic nuclear factor in the liver and are involved in the gene transcription of several enzymes. For example, increased influx of free fatty acids into the liver has been shown to induce enhanced gene transcription of hepatic acyl-coenzyme A synthetase, one of the limiting enzymes of triglyceride synthesis, as well as of microsomal triglyceride transfer protein (a rate limiting protein involved in the secretion of VLDLs), contributing to the development of hypertriglyceridemia.[63] Visceral fat accumulation is also associated with the enhanced expression of aquaporin adipose, an adipocyte-specific glycerol channel, which results in increased glycerol release from VAT.[64] This increased glycerol release is taken up by the liver through a liver-specific aquaporin, AQP-9, and converted into glycerol phosphate by glycerokinase and other enzymes as one of the mechanisms contributing to hyperglycaemia.[63–65]

Excess VAT induces inflammation

The expanded VAT becomes inflamed because of the infiltration of macrophages among hypertrophied adipocytes, leading to increased production of inflammatory cytokines (such as tumour necrosis factor α and interleukin 6) and reduced production of a protective adipokine, adiponectin. Adiponectin is an anti-atherogenic, anti-diabetic, and anti-inflammatory

protein, which is abundantly released from both SAT and VAT, but excess VAT is associated with the decreased production of adiponectin in whole-body adipose tissues, probably because of the increased secretion of inflammatory adipokines.[66] Dietary omega-3 long-chain polyunsaturated fatty acids have been shown to modify visceral and ectopic fat and inflammatory mediators in obese rats.[67] An extensive discussion of the emerging interplay between omega-3 fatty acids, ectopic adipose tissue, inflammation, and immunometabolism is beyond the scope of this position statement, but has been extensively reviewed elsewhere.[68]

VAT is a marker of increased ectopic fat

In response to excess triglycerides, the insufficient ability of SAT to expand through hyperplasia and to act as a protective metabolic sink in the context of a positive energy balance (resulting from excessive caloric intake, reduced energy expenditure due to physical inactivity, or a combination of these two components of the energy balance equation) causes lipid deposition in tissues that are not otherwise designed for adipose storage. This lipid spillover leads to lipid accumulation in normally lean tissues such as the liver, the heart (pericardial, epicardial, and intramyocardial), and skeletal muscle—a process known as ectopic fat deposition. In this context, excess visceral adiposity is a hallmark feature of dysfunctional SAT, a concept now widely recognised in the field of regional body fat distribution.[69,70]

Ectopic fat and health risk: marker or mediator?

There is an unresolved debate that is clinically relevant about the respective contributions of various ectopic fat depots (eg, liver, heart, muscle, pancreas, and kidney) to the dysmetabolic state and health complications associated with an excess of VAT. Perhaps the most hotly debated issue concerns liver fat. There are robust data showing that excess liver fat (for which non-alcoholic fatty liver disease [NAFLD] is a common clinical manifestation) is associated with most of the metabolic and inflammatory complications of visceral obesity.[71–74] For example, in one study,[75] a high sugar diet altered the VLDL kinetics such that there were statistically significant differences in the production and catabolic rates of VLDL subclasses between men with NAFLD and controls, in response to the high and low sugar diets. Men with NAFLD had higher plasma concentrations of VLDL1-triacylglycerol (TAG) after the high and low sugar diets, a lower VLDL1-TAG fractional catabolic rate after the high sugar diet, and a higher VLDL1-TAG production rate after the low sugar diet, than did controls. In that study, there were small changes in bodyweight, with both NAFLD and control groups gaining approximately 2 kg of bodyweight on the high sugar diet and losing approximately 2 kg on the low sugar diet. These small but statistically significant changes in bodyweight were related to changes in liver fat (measured by magnetic resonance spectroscopy [MRS])

but not to changes in VAT. These findings represent a situation in which diet can affect serum lipids and lipoprotein kinetics through weight-related or energy-related effects on liver fat, but these effects are independent of VAT. On the basis of these and other data, some investigators have suggested that most of the metabolic complications of visceral obesity are mediated by the metabolic derangements that accompany excess liver fat.[76,77] However, whether excess liver fat in isolation (ie, in the absence of excess VAT) is as detrimental as visceral obesity is not clear. Furthermore, the prevalence of NAFLD in isolation (without visceral obesity) is not well established.

Prospective observational studies have linked the presence of NAFLD with an increased risk of type 2 diabetes[78] and cardiovascular disease.[79] However, these observations are limited by heterogeneity with respect to how NAFLD was diagnosed (via different imaging techniques—eg, ultrasound, CT, or MRS—tests for altered liver enzymes, and [rarely] liver biopsy), by the limited ability to grade liver disease severity in epidemiological studies (steatosis to steato-hepatitis or non-alcoholic steatohepatitis [NASH] to fibrosis), and by the presence of concomitant deposits of visceral fat and their consequent metabolic derangements.

One possibility to explore the isolated role of excess liver fat on cardiometabolic risk is to test effects of genetic variants that predispose to cardiometabolic risk without the concomitance of other excess fat accumulation. Studies that tested the *PNPLA3* I148M variant, which commonly predisposes to NAFLD, showed inconsistent associations with incidence of major cardiovascular events.[80,81] The *TM6SF2* E167K variant also increases liver fat[82] and induces NASH and liver fibrosis[83] by reducing VLDL secretion and liver triglyceride export; yet, individuals with this variant have NAFLD but low concentrations of apolipoprotein B-containing lipoproteins in the blood. A Mendelian randomisation study done in a Danish population[80] did not establish a causal association between NAFLD and cardiovascular disease by testing variants in the *TM6SF2* gene. A meta-analysis done as part of the same investigation,[80] which included data from the Danish population and the CARDIoGRAMplusC4D consortium, reached similar conclusions.

An important clinical caveat of the concept of NALFD independently predisposing to increased cardiometabolic risk is that there is no evidence that its diagnosis will further add to risk stratification and subsequent management in addition to usual measures of excess adiposity, such as BMI and waist circumference. Certainly, from the hepatologist's perspective, the association of NAFLD with hepatic complications such as fibrosis, cirrhosis, and hepatocellular carcinoma needs to be seriously considered, and there is an unmet need for treatments that reduce liver fat accumulation and NASH.[84] Such treatments might also have the potential

to mitigate downstream cardiometabolic risk, although prospective studies will be needed to investigate this possibility.

The relative contributions of the various ectopic fat depots to the risk of complications might depend on the health outcome considered, with some depots having local effects and others contributing to systemic effects (or both).[17,73,85] For example, excess pericardial and epicardial fat is associated with atherosclerotic cardio-vascular disease[86] and atrial fibrillation.[87] The close proximity of the ectopic fat depot to the coronary arteries and atrial myocardium (and conduction system) might predispose to cardiac-specific health risks because of local, paracrine, effects of lipotoxicity.[88] However, excess pericardial and epicardial fat in isolation is much less common than its form associated with visceral obesity, making it difficult to determine its independent contribution to cardiac outcomes. For now, excess visceral adiposity could represent a useful indicator of an atherogenic and diabetogenic pattern of body fat distribution and a marker of dysfunctional SAT, making visceral adiposity an important target for diagnosis and treatment.

Do visceral and ectopic fat respond to treatment?

Evidence from several reviews and meta-analyses suggests that a decrease in energy intake or an increase in energy expenditure is associated with a reduction in VAT and SAT.[89–96] A meta-analysis by Sabag and colleagues,[95] showed that aerobic type exercise was associated with a significant reduction in VAT in adults with type 2 diabetes. Similarly, Verheggen and colleagues[96] did a meta-analysis wherein eight studies compared a hypocaloric diet with exercise. Although both strategies were associated with significant reductions in VAT, a 5% loss in bodyweight was associated with a 21% reduction in VAT after exercise, whereas only a 13% reduction in VAT was observed with a hypocaloric diet. A review by Hammond and colleagues[90] concludes that exercise of moderate to high intensity (50–70% VO_2 peak) in adults is associated with substantial reductions in VAT and SAT.

Several randomised controlled trials have assessed whether the reduction in abdominal fat depots in adults differs in response to diet-induced or exercise-induced weight loss when the negative energy balance induced by diet or exercise is matched.[97,98] Irrespective of sex, weight loss of about 7% was associated with a reduction in VAT of about 25% in response to diet or exercise. These observations are consistent with the review of Verheggen and colleagues,[96] wherein the results from eight studies in adults showed that diet and exercise are associated with similar reductions in VAT when the negative energy balance is matched. Irrespective of age, sex, or race, a negative energy balance induced by diet or exercise is generally associated with reductions in both VAT and SAT.[90,91,93,99] However, the response of VAT and SAT depends on how their changes are expressed. If the reduction in either depot is expressed in absolute measures (eg, reduction in cm³), generally men lose more VAT than do women, because men have more VAT at baseline.[96,100] Similarly, because women generally have more abdominal SAT than men, the reduction in SAT (cm³) in response to diet or exercise is greater in women than it is in men. However, if changes in SAT or VAT are expressed relative to baseline measures (eg, percentage reduction), the reduction in both adipose tissue depots is similar in men and women.

The evidence is mixed on the issue of whether a dose-response relation exists between exercise and reduction in VAT and SAT.[41,42,90,93,100,101] Studies that have examined the effect of exercise dose generally support the conclusion that increasing exercise-induced energy expenditure is positively associated with corresponding reductions in VAT and SAT.[42,90,94] Of particular interest to clinicians, several studies have shown clinically significant VAT reduction in response to exercise in the absence of substantial weight loss.[91,96] Gepner and colleagues reported the results of an 18-month randomised controlled trial among 278 sedentary adults with abdominal obesity or dyslipidaemia in a single workplace setting in Israel.[102] Participants were randomly assigned to a Mediterranean and low-carbohydrate diet (plus 28 g walnuts per day) or an isocaloric low-fat diet, with or without added moderate physical activity (80% aerobic; supervised with free gym membership). 240 (86%) participants completed the trial but all participants were included in the intention to treat analysis. Although both groups had similar moderate weight loss, VAT (22%), intrahepatic (29%), and intrapericardial (11%) fat losses were greater than pancreatic and femur intermuscular fat losses (1–2%). The Mediterranean and low-carbohydrate diet was better than the low-fat diet in decreasing intrahepatic, intrapericardial, and pancreatic fats; the addition of physical activity to either diet led to a significant decrease in VAT (mean difference –6·67 cm², 95% CI –14·8 to –0·45), independent of weight loss. This trial provides robust evidence that moderate weight loss alone inadequately reflects the important effects of lifestyle interventions on atherogenic and diabetogenic fat depots, the Mediterranean diet seems to mobilise specific ectopic fat depots, and exercise independently contributes to VAT loss.

Although the evidence clearly establishes that regular exercise combined with a healthy diet is associated with a substantial reduction in VAT independent of age, sex, and ethnic origin,[42,103,104] the separate effects of exercise amount and intensity on VAT are less clear. Findings from systematic reviews suggest that exercise amount—energy expenditure defined by metabolic equivalent of task-h per week[104] or kcals[42]—is positively associated with reductions in VAT.[104] However, the findings from the few randomised trials specifically designed to examine the independent contributions of exercise-induced energy

expenditure on VAT report findings to the contrary—that an increase in exercise amount is not positively associated with VAT reduction. In a trial of inactive adults with overweight or obesity, Keating and colleagues reported that exercise conditions varying in total time resulted in VAT reductions of a similar magnitude.[105] Similarly, in another trial, Slentz and colleagues reported that there was no difference in VAT reduction between groups that vary in exercise amount among adults with obesity.[106] These observations were supported by findings from the trial by Cowan and colleagues, who reported that increasing exercise amount without changes in energy intake for 6 months was not associated with increased VAT reduction in adults with abdominal obesity.[107]

Whether exercise intensity is associated with VAT reduction independent of exercise amount is also unclear. Whereas the primary finding from a review that compared exercise groups that varied in exercise intensity across studies suggests that intensity is positively associated with reductions in VAT,[100] preliminary findings from randomised trials are inconclusive. Similar to observations for exercise amount, Keating and colleagues, Slentz and colleagues, Cowan and colleagues, and Irving and colleagues reported no statistically significant effect of increasing exercise intensity on VAT reduction.[105–08]

Cowan and colleagues[107] considered whether the separate effects of exercise amount and intensity on VAT reduction differed across the abdominal region by analysing the change in VAT for five magnetic resonance images, extending from below to above L4–5 (figure 3). The two major observations from this analysis were that a substantial reduction in VAT occurs in response to exercise combined with a balanced diet (ie, participants do not eat more food to compensate for energy lost via exercise) irrespective of amount or intensity, and that the reduction in VAT is uniform across the abdomen.[107]

In summary, exercise and dietary interventions are associated with reduction in VAT, irrespective of amount or intensity of exercise. A weight loss of about 5% resulting from a lifestyle-based strategy consistent with current recommendations is likely to result in a 15–25% reduction in VAT.[90,96,97,98] These observations provide treatment options to target VAT reduction as part of a comprehensive lifestyle-based strategy to reduce health risk.

Although intervention studies have shown that loss of VAT is associated with cardiometabolic benefits among individuals with excess visceral adiposity, public health education and clinical approaches still focus on assessing the risk of obesity by BMI and on assessing the success of its management by the magnitude of weight loss achieved. In Japan, investigators of the longitudinal Amagasaki Visceral Fat Study have explored the relevance of classifying individuals not only on the basis of their BMI but also on the basis of their estimated level of VAT.[109] Several reports have been published on this study.[109–11] Overall, findings indicate that changes in weight and VAT observed (no change or
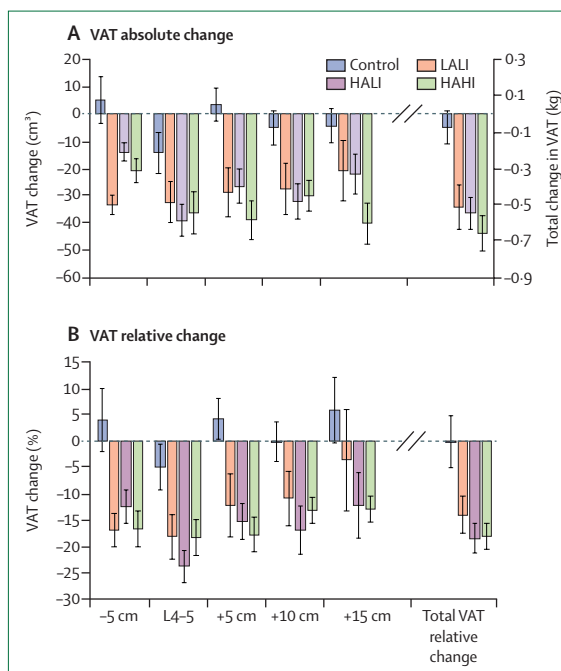

Figure 3: **Regional differences in VAT reduction across the abdomen in response to exercise of varying amounts and intensities**
Data shown are mean values and error bars are the associated standard error of the means. The MRI measures were taken before and after intervention (24 weeks). Absolute (cm^3; A) and relative (%; B) changes in VAT are shown at the L4–5 intervertebral space; 5 cm below L4–5; and 5 cm, 10 cm, and 15 cm above L4–5. Total VAT change (the sum of each individual slice) is also shown—for absolute change, total change is shown in kg; for relative change, total changes are percentage values. Reproduced from Cowan and colleagues,[107] by permission of Wiley-Blackwell on behalf of The Obesity Society. VAT=visceral adipose tissue. Control=no exercise. LALI=low amount, low-intensity exercise (180 kcal/session for women and 300 kcal/session for men, at 50% VO_2 peak). HALI=high amount, low-intensity exercise (360 kcal/session for women and 600 kcal/session for men, at 50% VO_2 peak). HAHI=high amount, high-intensity exercise (360 for kcal/session women and 600 kcal/session for men, at 75% VO_2 peak).

increase *vs* decrease) in response to a health promotion and education programme focussing on the importance of VAT were associated with corresponding changes (deterioration or improvement) in variables reflecting cardiometabolic risk. Also, individuals who initially had the highest level of VAT for their BMI benefited the most from the health promotion programme. Although this longitudinal study was not powered to compare cardiovascular disease outcomes between participants who lost VAT versus those who gained VAT, investigators found a lower cumulative incidence of cardiovascular outcomes among participants who lost VAT compared with those who gained VAT over the 50-month follow-up of the study.[109] Although these findings cannot quantify the respective contributions of weight loss versus loss of VAT, they highlight the potential relevance of monitoring visceral adiposity in cardiometabolic risk assessment and management. Large-scale cardiometabolic imaging studies that are underway should help to address this question.

Conclusions

Although the link between BMI and morbidity and mortality risk is firmly established at the population level, considerable variation exists at the individual level in the cardiometabolic risk profile in people with the same BMI. Many findings from CT and MRI studies have shown the limitations of BMI as a clinical tool to identify overweight and obese individuals with excess VAT, who represent the subgroup of individuals at highest cardiometabolic risk. Additionally, at any BMI value, excess visceral adiposity is often associated with an increased accumulation of lipids in normally lean tissues such as the heart, liver, and skeletal muscle, a harmful condition referred to as ectopic fat deposition.

Despite clear and convincing evidence that the accumulation of visceral and ectopic fat is a major contributor to cardiovascular disease and metabolic risk above and beyond BMI, the assessment of fat distribution in clinical practice remains a challenge. There is therefore a need to develop methods to identify individuals with excess visceral adiposity and ectopic fat in clinical practice and in public health programmes that would go beyond tracking and targeting BMI at the population level. Since VAT is the most diabetogenic and atherogenic fat depot, there is a need to develop simple, clinically applicable tools to be able to monitor changes in VAT and ectopic fat over time. Addition of the measurement of plasma triglyceride concentrations to the measurement of waist circumference (to identify hypertriglyceridemic waist)[34] might be helpful, but more refined tools that are validated with imaging data should be developed to further refine the definition of high-risk overweight and obesity.

Anthropometric indices of obesity are easily implemented, but newer imaging-based methods offer improved sensitivity and specificity for measuring specific depots. Lifestyle, pharmacologic, and surgical interventions permit a multidisciplinary approach to target visceral and ectopic fat that might improve outcomes. Finally, researchers and clinicians need to align the evidence with a public health message to focus on visceral and ectopic fat in addition to excess bodyweight to better combat the growing epidemic of obesity worldwide.

Search strategy and selection criteria

This position statement is a narrative review designed to provide a consensus perspective of the International Atherosclerosis Society and International Chair on Cardiometabolic Risk Working Group on Visceral Obesity. First, the group initially had a face-to-face meeting on April 24, 2017, to review the high-quality evidence available known to the subject experts. No formal comprehensive literature search was done because this Review is a joint consensus position statement rather than a formal literature review. After discussion and deliberation among the group regarding the context and quality of the evidence, an executive writing group was formed and was responsible for writing the first draft. This draft was then circulated to all authors for critical revision of intellectual content pertinent to each authors' expertise. High-quality published literature that became available after the initial face-to-face meeting (until Dec 31, 2018) was identified by all authors and reviewed by the executive writing group for inclusion in the manuscript. The first author coordinated the final preparation and submission of the position statement after the group achieved consensus and approved its content.

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