Endocrine-Related Cancer

The clinical importance of quantifying body fat distribution during androgen deprivation therapy for prostate cancer

Stephen J Foulkes, Robin M Daly and **Steve F Fraser**

Institute for Physical Activity and Nutrition, School of Exercise and Nutrition Sciences, Deakin University, Geelong, Australia

Correspondence
should be addressed
to S J Foulkes
Email
steve.foulkes@deakin.edu.au

Abstract

Androgen deprivation therapy (ADT) is now considered a mainstay in the treatment of metastatic and locally advanced prostate cancer (PCa). Despite well-established benefits of ADT in relation to overall survival, this treatment has been associated with a number of adverse effects, particularly with regard to key cardiometabolic risk factors including the development of insulin resistance, dyslipidemia and increases in total and regional fat mass. In non-ADT populations, increased levels of visceral adipose tissue (VAT) are thought to be a key mediator of the increased cardiometabolic risk associated with weight gain, but this has received limited attention in men treated with ADT. VAT is best assessed using tools such as computed tomography or magnetic resonance imaging; however, these tools are not readily accessible for the majority of researchers or clinicians. Recent advances allow for a method of estimating VAT using a whole-body dual-energy X-ray absorptiometry (DXA) scan that shows promise as a practical tool for researchers to evaluate changes in body fat distribution during ADT. The aim of this narrative review is to (1) review the available evidence with regard to the relationship between ADT and cardiometabolic risk; (2) discuss the role of body fat distribution on cardiometabolic risk in non-ADT populations, with a particular emphasis on the importance of visceral adiposity; (3) examine the potential influence of ADT on body fat distribution and visceral adiposity and (4) provide an overview of current tools used to measure changes in body fat distribution in men treated with ADT, highlighting the potential utility of a recently developed DXA-derived measure of VAT.

Introduction

Prostate cancer (PCa) is the primary cause of male cancer within developed nations (Torre *et al*. 2015). The five-year relative survival for PCa is now approaching 100% (DeSantis *et al*. 2014, Siegel *et al*. 2015), which can be attributed to improvements in detection and treatment of PCa. With more men surviving longer after their cancer diagnosis, there is greater emphasis for

health professionals to address non-cancer sources of morbidity and mortality, particularly those that could be related to the adverse effects of cancer treatment (Gomella *et al*. 2009). Androgen deprivation therapy (ADT) is a commonly prescribed treatment for slowing progression of metastatic PCa and has proven survival benefits when combined with radiation therapy in

men with locally advanced PCa (Heidenreich *et al.* 2014, Mohler *et al.* 2014). Over the past two decades, there has been progressive increase in the number of men receiving ADT treatment (Gilbert *et al.* 2011, Grossmann *et al.* 2011, Connolly *et al.* 2012); however, with the development of alternate regimes such as intermittent ADT and modifications to medical reimbursement schemes, use of continuous ADT may now be plateauing or possibly even declining (Tsai *et al.* 2015*b*, Liede *et al.* 2016). Regardless, the severe hypogonadism that occurs as a result of treatment has been associated with multiple adverse effects on musculoskeletal and cardiometabolic health, cognition, sexual health and function (Grossmann *et al.* 2011, Shastri & Yaturu 2011, Ahmadi & Daneshmand 2013, Nguyen *et al.* 2015). Evidence from observational cohort studies indicate that men undergoing ADT are at 11–31% increased risk of developing cardiovascular disease (CVD) (Keating *et al.* 2006, 2010, Saigal *et al.* 2007, Jespersen *et al.* 2014) and 16–61% increased risk of developing type 2 diabetes (Keating *et al.* 2006, 2010, Alibhai *et al.* 2009, Tsai *et al.* 2015*a*). In addition, evidence from prospective studies has shown that ADT is associated with increases in insulin resistance, dyslipidemia and total adiposity (Galvão *et al.* 2008, Hamilton *et al.* 2011, Morote *et al.* 2015). This is particularly concerning given that CVD is the primary cause of non-cancer mortality for men diagnosed with PCa (Lu-Yao *et al.* 2004, Ketchandji *et al.* 2009, Riihimäki *et al.* 2011). Identifying and addressing the adverse cardiometabolic effects associated with ADT is therefore an important consideration for the treating physician. Understanding the factors responsible for the increased cardiometabolic risk occurring as a result of ADT will allow physicians and health care professionals to identify those at greater risk of cardiometabolic disorders, which should prompt an early intervention in the treatment process.

Evidence from non-ADT populations has consistently shown that obesity and fat mass are important mediators of cardiometabolic risk; however, this relationship is influenced by the distribution within distinct depots of adipose tissue (Cornier *et al.* 2011). The accumulation of fat mass within the abdominal region (Snijder *et al.* 2004*b*, Ghandehari *et al.* 2008), specifically within visceral adipose tissue (VAT) (Liu *et al.* 2010, Kaess *et al.* 2012, Nazare *et al.* 2012, Smith *et al.* 2012) is thought to be particularly deleterious for cardiometabolic health. Computed tomography (CT) and magnetic resonance imaging (MRI) are considered gold standards for the

assessment of VAT (Cornier *et al.* 2011); however, these tools are expensive, require a specialized operator, and may not be easily accessible. Therefore, alternative tools that can accurately quantify VAT, whilst being accessible and economically viable for assessing a large number of patients are required.

Recent advances in DXA technology have led to the development of software that can predict abdominal subcutaneous adipose tissue (SAT) and VAT from a whole-body scan (Kaul *et al.* 2012), and this has recently been validated against CT in men undergoing ADT (Cheung *et al.* 2016*a*). Whilst ADT has been associated with gains in abdominal fat mass, there are conflicting reports as to whether this is due to changes in SAT and/or VAT (Smith *et al.* 2002, 2008*b*, Hamilton *et al.* 2011, Cheung *et al.* 2016*b*). Thus, further research is needed using direct measures of quantifying abdominal adipose tissue to provide evidence regarding the relationship between ADT and cardiometabolic risk and if changes in body fat distribution during treatment are contributing to this increased risk, thereby allowing for earlier and more-targeted intervention. Furthermore, given the greater practicality and feasibility of using a DXA-derived assessment of SAT and VAT, the accuracy and clinical utility of this measure requires further investigation.

The following narrative review aims to (1) explore the relationship between ADT and cardiometabolic risk; (2) discuss the role of body fat distribution on cardiometabolic risk in non-ADT populations, with a particular emphasis on the importance of visceral adiposity; (3) examine the potential influence of ADT on body fat distribution and visceral adiposity and (4) provide an overview of current tools used to quantify body fat distribution in men treated with ADT, highlighting the conceivable role of a DXA-derived measure of VAT in informing clinical decision making within this population.

Effect of androgen deprivation therapy on cardiometabolic risk

Evidence from both prospective and population-based studies has established a relationship between ADT and a number of adverse effects that increase the risk of CVD and type 2 diabetes (Grossmann *et al.* 2011, Nguyen *et al.* 2015). This led to the American Heart Association releasing a statement in 2010 highlighting the potential link between ADT and increased risk of CVD (Levine *et al.* 2010). This statement also emphasizes that clinicians periodically evaluate and monitor

key cardiometabolic risk factors in their patients (Levine *et al.* 2010). This requires that clinicians have a sound understanding of the influence of ADT on cardiometabolic functioning and factors that may be mediating this process.

Insulin resistance and glucose regulation

There is mounting evidence that ADT treatment may contribute to the development of type 2 diabetes, through an initial increase in insulin resistance, followed by a progressive worsening of glycemic control (summarized in Table 1). In a cross-sectional study comparing 18 men with PCa who had undergone at least 12 months of ADT compared to 17 men with PCa who were ADT naïve and 18 age-matched controls without PCa, those treated with ADT had significantly higher levels of fasting insulin, glucose and insulin resistance, as measured by the homeostatic model assessment of insulin resistance (HOMA-IR), even after adjustment for age and BMI (Basaria *et al.* 2006). Prospective studies have demonstrated increases in fasting insulin ranging from 26 to 63% (Smith *et al.* 2001, 2008*a*, Dockery *et al.* 2003), increases in HOMA-IR of up to 27% (Cheung *et al.* 2016*b*) and decrements in insulin sensitivity of 13% (measured by insulin sensitivity index) (Smith *et al.* 2006, 2008*a*) following at least 12 weeks of ADT. Observations from short-term administration of ADT (<12 weeks) have demonstrated variable effects on plasma glucose, with some studies showing significant increases (Smith *et al.* 2006) and others showing no change (Smith *et al.* 2001, Dockery *et al.* 2003). Longitudinal studies with follow-up periods beyond 12 months have shown 5–10% increases in fasting glucose (Ziaran *et al.* 2013, Morote *et al.* 2015). Although studies investigating

changes in HbA1c have shown little to no change in HbA1c during the first 6–12 months of ADT (Smith *et al.* 2006, Hamilton *et al.* 2011, Phillips *et al.* 2014, Morote *et al.* 2015), given that changes in plasma glucose do not tend to appear until at least 12 months of treatment, studies with longer follow-up periods may be required to adequately assess the effect of ADT on this measure. This discrepancy between short- and long-term studies may be explained by a relative compensatory hyperinsulinemia occurring after the onset of ADT, which is initially able to maintain euglycemia (Kahn *et al.* 2014). However, with continued insulin resistance, pancreatic insulin release is no longer sufficient to maintain euglycemia, with the end result being impaired fasting glucose (Kahn *et al.* 2014).

Changes in lipid profile

As summarized in Table 2, there is considerable evidence indicating that ADT adversely affects blood lipid profiles. Cross-sectional studies of men with PCa undergoing ADT reported significantly higher levels of triglycerides, total cholesterol, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol compared to ADT-naïve and age-matched controls (Basaria *et al.* 2002, Cleffi *et al.* 2011). Results from prospective studies assessing changes in lipids over the first 3–12 months of ADT have shown a greater level of variability, with some studies reporting increases in triglycerides (27–46%) (Smith *et al.* 2002, 2006, Hamilton *et al.* 2011, Morote *et al.* 2015), LDL cholesterol (3–10%) (Smith *et al.* 2002, Morote *et al.* 2015, Oka *et al.* 2015) and HDL cholesterol (8–20%) (Dockery *et al.* 2003, Smith *et al.* 2006, Morote *et al.* 2015), whereas others have reported no change (Smith *et al.* 2001, 2006, Dockery *et al.* 2003, Hamilton *et al.* 2011,

Table 1 Results from studies investigating the effect of ADT on insulin and glucose homeostasis.

Study	n	Comparison groups	Duration	Fasting glucose (%)	Fasting insulin (%)	Insulin resistance (%)
Cross-sectional studies						
Basaria *et al.* (2006)	18	PCa controls (*n*=17) Non-PCa controls (*n*=18)	>12 months of ADT use	+26.0–26.5*	+50.9–76.2*	+70.0–84.4[a],*
Prospective studies						
Smith *et al.* (2001)	22	None	3 months	+3.5 (ns)	+63.6*	NR
Smith *et al.* (2006, 2008*a*)	25	None	12 weeks	+2.0 (ns)	+25.9*	+12.9[b],*
Dockery *et al.* (2003)	16	None	3 months	+7.1 (ns)	+64.6*	NR
Hamilton *et al.* (2011)	26	None	12 months	+0.3 (ns)	NR	+11.6[a],*
Ziaran *et al.* (2013)	95	Non-PCa controls (*n*=88)	24 months	+11.3*	NR	NR
Morote *et al.* (2015)	539	None	12 months	+4.7*	NR	NR

*Denotes significant difference ($P < 0.05$), [a]assessed via HOMA-IR, [b]assessed via insulin sensitivity index.
ADT, androgen deprivation therapy; NR, not reported; ns, not significant; PCa, prostate cancer.

Table 2 Results from studies investigating the effect of ADT on plasma lipids.

Study	n	Comparison groups	Duration	Total cholesterol (%)	LDL-cholesterol (%)	HDL-cholesterol (%)	Triglycerides (%)
Cross-sectional studies							
Basaria et al. (2002)	20	PCa controls (n = 18) Non-PCa controls (n = 20)	45 months[a]	+7.4–12.9 (ns)	+9.1–18.2 (ns)	−8.3 (ns)	+15–35*
Cleffi et al. (2011)	54	PCa controls (n = 25)	15 months[a]	+10.5*	+15.0*	+8.1 (ns)	−12.3 (ns)
Prospective studies							
Smith et al. (2001)	22	None	3 months	+3.2 (ns)	−2.3 (ns)	+8.3 (ns)	+13.3 (ns)
Smith et al. (2002)	32	None	48 weeks	+9.0*	+7.3*	+11.3*	+26.5*
Smith et al. (2006)	26	None	12 weeks	+9.4*	+8.7 (ns)	+9.9*	+23.0*
Smith et al. (2008b)	26	None	12 months	NR	NR	+9.7*	+19.4 (ns)
Dockery et al. (2003)	16	None	3 months	+7.3*	+0.3 (ns)	+20.0*	+14.6 (ns)
Hamilton et al. (2011)	26	None	12 months	+11.2*	+8.9 (ns)	+2.3 (ns)	+46.6*
Oka et al. (2015)	58	None	6 months	+11.2*	+10.3*	+15.2*	+0.6 (ns)
Morote et al. (2015)	539	None	12 months	+5.8*	+3.0*	+7.7*	+12.6*

*Denotes significant difference (P < 0.05), [a]mean duration of ADT.
ADT, androgen deprivation therapy; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NR, not reported; ns, not significant; PCa, prostate cancer.

Oka et al. 2015). In a large multicenter intervention trial consisting of 539 men undergoing 12 months of ADT, Morote et al. (2015) found that ADT treatment was associated with increases in HDL and LDL cholesterol and triglycerides by 8.5, 2.9 and 6.9%, respectively, within 6 months of treatment; triglycerides increased by a further 6% at 12 months (Morote et al. 2015). Although increases in HDL cholesterol are thought to be cardio-protective in non-ADT populations, there is doubt if this is the case in ADT-treated men as there is some evidence that testosterone may increase reverse cholesterol transport from macrophages in vivo (Langer et al. 2002), whereas congenital hypogonadism has been associated with a lower proportion of the anti-atherogenic HDL cholesterol subfraction (Bolu et al. 2013). Given the lack of consistency seen within the literature, it is important that clinicians routinely monitor the blood lipid profile in individual patients to identify those who develop dyslipidemia. Further research identifying potential mediators of the ADT-associated dyslipidemia is also needed to allow for early intervention before clinically significant changes occur.

Changes in blood pressure

Treatment with ADT does not appear to increase blood pressure, with no cross-sectional or longitudinal studies over 3–12 months finding significant changes in either systolic or diastolic blood pressure (Smith et al. 2001,

Cleffi et al. 2011, Hamilton et al. 2011, Morote et al. 2015). A small study of 22 men reported increases in arterial stiffness after three months of ADT (Smith et al. 2001), but there were no significant changes in blood pressure. Given the lack of change seen in other studies, this increase in arterial stiffness may not be of sufficient magnitude to negatively affect blood pressure.

Cardiovascular disease and diabetes

Given the evidence linking ADT to changes in a number of cardiometabolic risk factors, it seems reasonable that ADT could be related to accelerated development of cardiometabolic conditions such as CVD and type 2 diabetes. In non-ADT-treated individuals, increases in insulin resistance, LDL cholesterol and triglycerides have been implicated in the pathogenesis of CVD primarily through their effects on atherosclerotic plaque development (Paneni et al. 2013, Weber & Noels 2011). Additionally, insulin resistance is a major precursor to the development of type 2 diabetes (Kahn et al. 2014). However, it remains unclear whether ADT results in a significant increase in morbidity and mortality from CVD and type 2 diabetes. Evidence from large observational studies show that after adjustment for other covariates such as age, ethnicity and other comorbidities, men treated with ADT are at 16–61% increased risk of type 2 diabetes (Keating et al. 2006, 2010, Alibhai et al. 2009, Tsai et al. 2015a) and 11–31% increased risk of CVD

morbidity (Keating *et al.* 2006, 2010, Saigal *et al.* 2007, Jespersen *et al.* 2014, O'Farrell *et al.* 2015) including non-fatal myocardial infarction (11–31%) (Keating *et al.* 2006, 2010, Jespersen *et al.* 2014), coronary heart disease (16–19%) (Keating *et al.* 2006, 2010) and stroke (19–22%) (Keating *et al.* 2010, Jespersen *et al.* 2014) and 16–35% increased risk of cardiovascular mortality (Keating *et al.* 2006, 2010, Jespersen *et al.* 2014). However, the results from some of these studies are limited by their reliance on the accurate reporting of CVD events and lack of a non-ADT control group. Therefore, it is difficult to determine whether ADT alone, or other confounding factors, are contributing to this increased disease risk. Interestingly a meta-analysis of 4141 patients from eight RCTs comparing men randomized to ADT vs no ADT failed to find an association between ADT and cardiovascular mortality (Nguyen *et al.* 2011). However, cardiovascular morbidity was not assessed in the included studies, and so these results cannot conclude that ADT is not associated with increased risk of non-fatal CVD. Another meta-analysis of 1316 patients from three RCTs examining the effect of ADT on non-fatal cardiovascular events reported a 55% greater risk of a non-fatal cardiovascular event with at least six months of ADT (Carneiro *et al.* 2015). Until further investigations are conducted to clarify the effect of ADT on cardiovascular morbidity and mortality, minimizing the potential for cardiovascular harm should be an important focus for the clinician.

An additional consideration when interpreting research investigating the link between ADT and cardiometabolic disease incidence is that none of the studies mentioned assessed changes in cardiometabolic risk factors or fat mass. Therefore, it is unclear whether the increase in risk is due to a direct effect of ADT on cardiovascular functioning or is mediated by its effects on cardiometabolic risk factors such as fat distribution. This is particularly important when trying to develop targeted screening and treatment strategies within this population. Understanding the effect of ADT on fat distribution may shed light on the link between ADT and increased cardiometabolic risk, and this relationship will be discussed in relation to both ADT and non-ADT populations.

Location matters: body fat distribution and cardiometabolic risk

Adiposity has a major influence on the risk of CVD and type 2 diabetes across genders, ethnicities and age groups (Cornier *et al.* 2011). At the population level, obesity (typically measured by body mass index (BMI)) has been shown to be positively associated with cardiometabolic risk factors such as hypertension (Brown *et al.* 2000, Cutler *et al.* 2008, Nguyen *et al.* 2008), dyslipidemia and insulin resistance (Brown *et al.* 2000, Nguyen *et al.* 2008), as well as incidence of CVD (Jonsson *et al.* 2002, Nguyen *et al.* 2008), type 2 diabetes (Nguyen *et al.* 2008) and the metabolic syndrome (Nguyen *et al.* 2008). However, adiposity is a heterogeneous condition and can be separated into distinct patterns of fat distribution that cannot be measured by BMI (Cornier *et al.* 2011, Booth *et al.* 2014). Different patterns of fat distribution have unique contributions to cardiometabolic risk, independent of total fat mass (Booth *et al.* 2014). The following discussion will explore the relationship between body fat distribution and cardiometabolic risk in ADT and non-ADT populations, how ADT affects body fat distribution and how these changes can be assessed.

Android and gynoid adiposity

Abdominal adiposity as measured by waist circumference or DXA has been shown to be consistently correlated with cardiometabolic risk factors including higher levels of insulin resistance and fasting glucose (Seidell *et al.* 2001, Snijder *et al.* 2004*a*,*b*, Ghandehari *et al.* 2008), dyslipidemia (Seidell *et al.* 2001, Snijder *et al.* 2004*a*, Ghandehari *et al.* 2008, Lee *et al.* 2008) and higher blood pressure (Ghandehari *et al.* 2008, Lee *et al.* 2008) and is associated with the development of CVD (Ghandehari *et al.* 2008, Arsenault *et al.* 2009, Emerging Risk Factors Collaboration 2011), stroke (Winter *et al.* 2008, Bodenant *et al.* 2011) and type 2 diabetes (Snijder *et al.* 2003, Lee *et al.* 2008), independently of other key covariates including BMI. Compared to android adiposity, having a greater amount of fat distributed in the lower body measured by hip/thigh circumference or DXA has been shown to be inversely associated with markers of dyslipidemia, insulin resistance and glucose control, independent of total or central adiposity (Seidell *et al.* 2001, Snijder *et al.* 2003, 2004*a*,*b*). This suggests that the propensity to store fat within this region may be cardioprotective.

There is growing evidence that sex hormones are key mediators of body fat distribution. Studies comparing males and females have shown that when matched for total fat mass, males have a greater amount of abdominal fat mass compared to both premenopausal and postmenopausal women (Kuk *et al.* 2005), suggesting

the presence of testosterone may encourage abdominal weight gain. However, low levels of circulating testosterone in males have been associated with the accumulation of abdominal fat mass (Couillard et al. 2000, Svartberg et al. 2004). Conversely, observational studies of testosterone supplementation in hypogonadal males have shown significant reductions in abdominal fat mass after treatment (Aversa et al. 2010, Kalinchenko et al. 2010, Saad et al. 2013). In contrast, RCTs investigating the effect of testosterone supplementation on VAT have shown inconsistent results, with some studies showing testosterone supplementation resulted in a reduction (Mårin et al. 1992, 1993) or attenuated the age-related increase in VAT (Allan et al. 2008), whereas others have shown reductions in SAT with no changes in VAT (Emmelot-Vonk et al. 2008, Frederiksen et al. 2012, Hoyos et al. 2012, Gianatti et al. 2014). Reasons for these discrepancies are unclear, but may relate to differences in the dose, route of administration and baseline circulating testosterone concentrations of study participants.

This suggests low testosterone levels could contribute to an increase in abdominal adipose tissue; however, whether this is due to an increase in abdominal SAT and/or VAT is unclear. Indeed, studies investigating the effect of ADT on abdominal adiposity have shown increases in waist circumference of 1.4–1.9% after 6–12 months of treatment (Hamilton et al. 2011, Morote et al. 2015). However, as these studies did not measure hip circumference, it is unclear if the increases represented a preferential accumulation of abdominal fat mass or were more representative of a global increase in adiposity. In 95 men treated with ADT, Ziaran and coworkers (Ziaran et al. 2013) reported a 7.5% and 12% increase in waist-to-hip ratio over the first 12 and 24 months of treatment, respectively, suggesting that there is a preferential accumulation of abdominal fat mass. However, these results need to be interpreted with caution as the waist-to-hip ratio cannot differentiate between absolute changes in fat mass and lean tissue mass. A decline in gluteofemoral muscle mass may also mask gains in gluteofemoral fat mass, thereby not altering hip circumference, resulting in a larger waist-to-hip ratio. This notion is supported in part by the results of Galvão and coworkers (Galvão et al. 2008) who assessed DXA-derived changes in regional fat and lean tissue mass in 76 men with PCa over the first 36 weeks of ADT treatment. In this study, the increases in fat mass were 21% and 19% in the upper and lower limbs, respectively, compared to 12% in the abdominal region, which suggests that ADT may lead to greater gains in appendicular fat mass. Furthermore, there were region-specific differences in the changes (losses) in lean tissue mass; abdominal 1.4%, upper limbs 3.7% and lower limbs 5.6%. This highlights that common anthropometric methods such as BMI and waist–hip ratio should be interpreted with caution when measuring changes in adiposity within this population, as they may underestimate changes in fat mass, particularly in the upper and lower limbs.

The role of visceral adipose tissue

Although there is evidence that global patterns of fat distribution are related to cardiometabolic risk, questions remain as to the unique contribution of different depots of adipose tissue. SAT is located underneath the skin and superficial to the abdominal wall, whereas VAT is located underneath the abdominal fascia, in close proximity to key metabolic organs such as the liver and pancreas (Cornier et al. 2011, Shuster et al. 2014). Evidence from both cross-sectional and longitudinal studies assessing abdominal fat distribution via CT or MRI in large non-ADT cohorts such as the Framingham Study and Multi-Ethnic Study of Atherosclerosis have shown positive associations between VAT and insulin resistance (Preis et al. 2010, Shah et al. 2014), abnormal glucose control (Liu et al. 2010, Smith et al. 2012, Shah et al. 2014), dyslipidemia (Liu et al. 2010, Smith et al. 2012, Shah et al. 2014, Hwang et al. 2015), systemic inflammation (Pou et al. 2007, Shah et al. 2014) and greater risk of CVD, type 2 diabetes and metabolic syndrome (Rosito et al. 2008, Pou et al. 2009, Liu et al. 2010, Smith et al. 2012, Shah et al. 2014), independent of age and BMI. In contrast, correlations between abdominal SAT and risk factors have been weaker (Pou et al. 2007, 2009, Preis et al. 2010) or non-existent (Smith et al. 2012, Shah et al. 2014, Hwang et al. 2015). This suggests that associations between abdominal adiposity and cardiometabolic risk are primarily related to an accumulation of VAT, although cause and effect cannot be established from the previously mentioned studies.

The mechanisms underlying the differing associations between abdominal VAT and SAT with cardiometabolic risk factors have not been fully elucidated; however, several theories have been proposed. In contrast to subcutaneous adipocytes, visceral adipocytes release greater amounts of free fatty acids and pro-inflammatory cytokines (Capurso & Capurso 2012, Booth et al. 2014), which have been implicated in the development and progression of many cardiometabolic diseases (Capurso & Capurso 2012).

Blood supply from subcutaneous adipocytes drains into the systemic circulation, whereas blood supply for VAT drains directly into the liver via the portal vein, thereby exposing the liver to significantly higher concentrations of these free fatty acids and pro-inflammatory cytokines that could result in impaired lipid and glucose metabolism within the liver (van der Poorten et al. 2008). Indeed, studies have found a significant correlation between VAT and accumulation of fat within the liver (Liu et al. 2011, Nazare et al. 2012). Given the important role of the liver in glucose and lipid regulation, this may explain part of the relationship between the accumulation of VAT and the development of insulin resistance and dyslipidemia (Hajer et al. 2008, van der Poorten et al. 2008, Capurso & Capurso 2012, Walker et al. 2014). A more recent theory also suggests increased VAT may be representative of an inability of the body to store excess lipids within SAT, resulting in a global accumulation of adipose tissue within ectopic sites such as the muscle, liver, pancreas and myocardium (Després 2012, Tchernof & Després 2013).

A number of the previously mentioned changes in cardiometabolic risk factors seen during ADT mirror those associated with increased visceral adiposity; however, few studies have attempted to directly assess the influence of ADT on abdominal adipose tissue depots or their associations with cardiometabolic risk (Table 3). Two studies (Smith et al. 2002, 2008b) have reported an 11–15% increase in abdominal SAT cross-sectional area measured by single-slice CT, with no significant change in VAT in 26–32 men undergoing 48–52 weeks of ADT. Cheung and coworkers (Cheung et al. 2016b) also failed to find an effect of ADT on VAT (measured via DXA) in 34 men over a 52-week follow-up period; however, changes in SAT were not reported. In contrast, results from a similarly sized cohort of men undergoing 52 weeks of ADT reported increases in CT-derived cross-sectional areas of abdominal SAT (17%) and VAT (22%), with changes occurring after at least 6 months (Hamilton et al. 2011). The reasons for these discrepant findings are unclear. Participants in the latter study (Hamilton et al. 2011)

had a greater level of adiposity at baseline which could have contributed to the differences seen in VAT between studies. Ageing, physical activity and diet are also associated with abdominal fat mass and VAT (Kuk et al. 2005, Molenaar et al. 2009, Nazare et al. 2013, Murabito et al. 2015), but these factors were not controlled for in three of the four studies conducted to date (Smith et al. 2002, 2008b, Hamilton et al. 2011). Cheung and coworkers (Cheung et al. 2016b) conducted the only study to include an age-matched non-ADT control group. However, as these authors used a DXA-derived estimate of VAT (rather than a direct assessment), a regulatory effect of ADT on VAT should not be discounted at this stage. Furthermore, given all four studies had relatively small sample sizes (between 26 and 34 men), larger sample sizes may have been needed to identify if there is a consistent effect of ADT on abdominal adipose tissue.

Interestingly, Hamilton and coworkers (Hamilton et al. 2011) also demonstrated that the increase in VAT during ADT was moderately correlated with increasing insulin resistance (measured via HOMA-IR), which was independent of changes in sex hormones. This suggests that increases in insulin resistance during ADT could be partly due to an indirect effect of changes in VAT during treatment. In contrast, no significant associations were found between abdominal SAT and insulin resistance after controlling for changes in sex hormones. This is an important finding, as it suggests that gains in VAT could be contributing to the increased cardiometabolic risk seen during ADT. However, the more recent study of Cheung and coworkers (Cheung et al. 2016b) (which also included a non-ADT control group) reported an increase in insulin resistance despite no change in VAT. This increase in insulin resistance was moderately correlated with the increase in fat mass; however, abdominal SAT was not reported in this study. Therefore, it is unclear if changes in insulin resistance were related to gains in abdominal SAT or changes in other compartments of adipose tissue.

In summary, the available data indicate that ADT appears to primarily cause the expansion of SAT, with

Table 3 Results from prospective studies investigating the effect of ADT on abdominal adipose tissue.

Study	n	Comparison groups	Duration	Assessment method	VAT (%)	SAT (%)
Smith et al. (2002)	32	None	48 weeks	Single-slice CT (L4–L5)	−0.3 (ns)	+11.1*
Smith et al. (2008b)	26	None	12 months	Single-slice CT (L4–L5)	+1.0 (ns)	+15.5*
Hamilton et al. (2011)	26	None	12 months	Single-slice CT (L4–L5)	+21.8*	+12.7*
Cheung et al. (2016b)	34	PCa controls (n = 29)	12 months	DXA	+1.9 (ns)	NR

*Denotes significant difference (P < 0.05).
ADT, androgen deprivation therapy; CT, computed tomography; DXA, dual-energy X-ray absorptiometry; NR, not reported; ns, not significant; PCa, prostate cancer; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

minimal impact on VAT. However, these findings should be interpreted with caution given the limitations of the studies conducted to date, including small sample sizes, lack of control groups or use of indirect measures to assess abdominal adipose tissue. Therefore, it appears that whilst being a plausible explanation linking ADT to increased risk of CVD and T2DM, further research using larger sample sizes and including non-ADT comparison groups is needed to establish the effect of ADT on body fat distribution and abdominal adipose tissue. This may help in identifying whether gains in fat mass associated with ADT are contributing to increased cardiometabolic risk or whether other factors such as a direct effect of ADT on metabolic organs such as the liver, pancreas and muscle tissue require further investigation.

Current methods of assessing body fat distribution during ADT

Commonly used measures of assessing body composition and fat distribution include waist and hip circumference, bioelectrical impedance analysis (BIA), DXA, CT and MRI (Cornier et al. 2011, Di Sebastiano & Mourtzakis 2012). As indicated in Table 4, all have advantages and disadvantages in their accuracy and practicality that must be taken into account when choosing the best tool to assess body composition and fat distribution.

Circumferences

Circumferences are a simple and rapid tool to estimate abdominal and lower body FM. Waist and hip circumference are used as a marker of abdominal and gluteofemoral fat, respectively (Cornier et al. 2011, Shuster et al. 2014); however, a key limitation is their inability to discriminate between differences in fat and lean body mass, as well as differences between discrete adipose tissue depots. Given the precise effect of ADT on the ratio between SAT and VAT is unclear, waist circumference may lack the necessary precision and sensitivity to accurately identify changes occurring in these depots.

Bioelectrical impedance analysis

BIA can be used to estimate FM and fat-free mass by measuring the resistance to a weak electrical current passed throughout the body (Kyle et al. 2004, Mialich et al. 2014). BIA has the advantages of being quick, easy to administer and portable (Mialich et al. 2014). However, its accuracy largely depends on the applicability of the prediction equation to the patient's age, gender, race, ethnicity and health status and hydration status (Dehghan & Merchant 2008, Jaffrin & Morel 2008, Mialich et al. 2014) and as it indirectly estimates fat mass from the conduction of electrical current through fat-free tissue, its ability to accurately measure changes in fat distribution appears somewhat limited (Shuster et al. 2014).

Computed tomography and magnetic resonance imaging

CT and MRI are considered the gold standard for the assessment of fat distribution (Cornier et al. 2011, Di Sebastiano & Mourtzakis 2012, Shuster et al. 2014). They provide a detailed cross-sectional slice of body tissues, and multiple slices can be taken to create a three-dimensional image of a given region (Cornier et al. 2011, Shuster et al. 2014). CT and MRI have the added value of being able to directly measure adipose tissue depots, making them the gold-standard tool for assessing VAT and SAT. However, they have reduced feasibility due to their high costs, need for specialized equipment and in the case of CT, relatively high radiation exposure (Cornier et al. 2011, Shuster et al. 2014). This often results in only a single slice being assessed and reduced accuracy when estimating volumes of adipose tissue (Shen et al. 2004, Demerath et al. 2007,

Table 4 Capability of different body composition measurement tools to assess global patterns of body fat distribution and distinct patterns of visceral and subcutaneous adipose tissue.

Method	Capability of measuring global fat distribution	Capability of measuring adipose tissue depots	Clinical applicability
Circumferences	High	Low	Very high
BIA	Low	Low	Very high
DXA	High	High	Moderate
CT	Very high	Very high	Low
MRI	Very high	Very high	Low

Adapted from Di Sebastiano et al. (2012) and Shuster et al. (2014).
BIA, bioelectrical impedance; circumferences, waist:hip; CT, computed tomography; DXA, dual-energy X-ray absorptiometry; MRI, magnetic resonance imaging.

Irlbeck *et al.* 2010, So *et al.* 2012*a*,*b*). Therefore, this may limit their practicality for many clinicians, health professionals and researchers looking to routinely quantify changes in abdominal adipose tissue during ADT, particularly in larger cohorts of patients.

DXA: a new tool for assessing visceral adiposity

DXA is used to estimate the relative amounts of total and regional fat mass, lean tissue mass and BMD (Bazzocchi *et al.* 2016). DXA has the advantage of being quick, relatively inexpensive and possesses a high level of precision, (coefficient of variation <3%) (Kaminsky *et al.* 2014). Studies comparing DXA to CT and MRI have also shown it to be a highly accurate measure of body composition ($r = 0.97$–0.99) (Kullberg *et al.* 2009). DXA can also accurately measure regional body composition, allowing the clinician to measure distinct changes in fat mass and lean tissue mass in the abdominal region (including android and gynoid), upper limb and lower limb. Although DXA involves exposure to ionizing radiation, the dose is minimal for a total body scan (<0.01 mSv) (Damilakis *et al.* 2010). Regardless, this should be taken into consideration when taking repeated measurements. An additional limitation is that extremely obese individuals may be too large to fit into the entire scanning field or may exceed the weight restrictions for the machine (~160 kg) (Bazzocchi *et al.* 2016).

Recent advances have led to the development of DXA software (CoreScan for Lunar and InnerCore for Hologic DXA systems) that is capable of estimating VAT and SAT volumes from a standard total body scan. This can be performed by measuring SAT volume within the android region of the body (a predetermined region of interest placed immediately above the iliac crest; Fig. 1i) and subtracting this from the total android fat mass. Scans from DXA systems using this software in non-ADT populations have shown strong correlations with gold standard abdominal SAT/VAT volumes measured by volumetric CT and MRI ($r = 0.90$–95) (Kaul *et al.* 2012, Cheung *et al.* 2016*a*, Neeland *et al.* 2016). The largest of these studies reported DXA-derived VAT mass was able to explain 82% (females) and 87% (males) of the variation in VAT mass measured by multi-slice MRI in a large ($n = 2689$) multi-ethnic sample with varying levels of adiposity measured by BMI. Cheung and coworkers (Cheung *et al.* 2016*a*) also compared VAT volume measured by DXA to VAT cross-sectional area at the L4–L5 vertebral disc
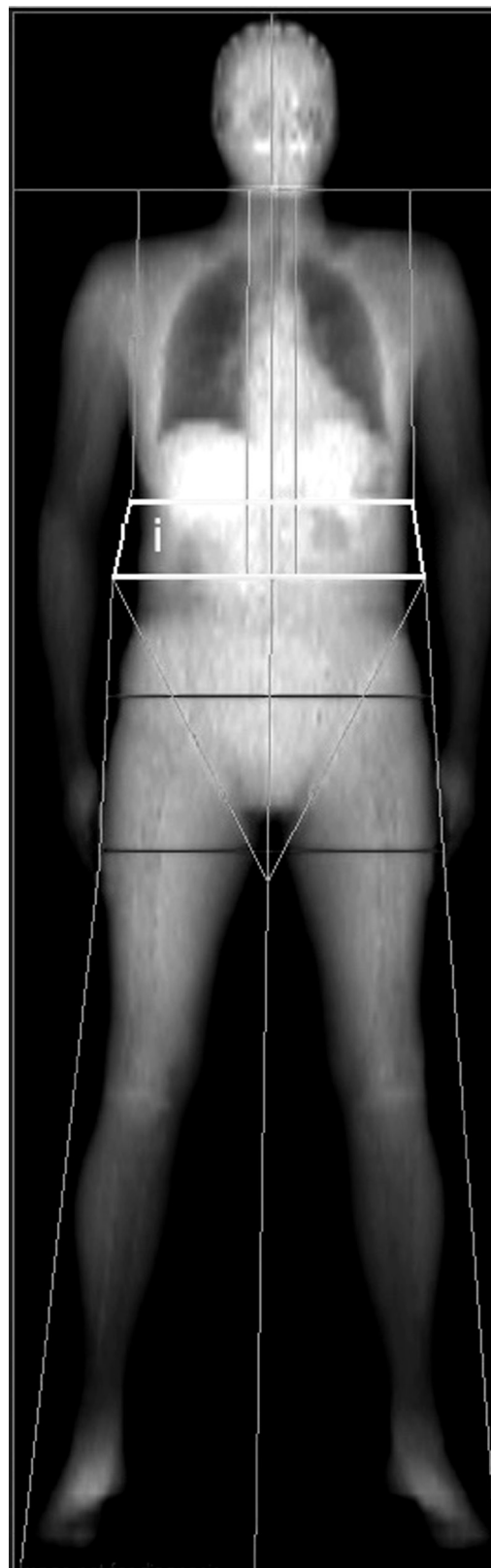

Figure 1
Whole body dual-energy X-ray absorptiometry (DXA) scan. (i) The android region of interest used to calculate android fat mass.

space measured by single-slice CT in 29 men with non-metastatic PCa undergoing 12 months of ADT. These authors reported a strong correlation between the two measures ($r=0.83$); however, this relationship was weaker than previous comparisons against multi-slice CT/MRI measurements (Kaul *et al.* 2012, Ergun *et al.* 2013). The weaker relationship reported in this study could have been influenced by reduced accuracy when using a single-slice CT measurement to assess VAT volumes (Shen *et al.* 2004) and/or the fact that the slice was taken at the L4–L5 vertebrae, which has been shown to have weaker associations with VAT volume than slices taken 5–10 cm above this location (Shen *et al.* 2004). However, as this study did not include gold standard volumetric measures of VAT/SAT, it cannot be excluded that DXA has reduced accuracy when assessing changes in VAT in this patient population. Collectively, these results suggest that VAT estimated from newly developed DXA software may be a sufficiently accurate, cost-effective and practical alternative to CT and MRI for estimating abdominal SAT and VAT in ADT-treated men. However, further research is required to gauge the ability of DXA to assess changes in abdominal adipose tissue during ADT compared to gold standard volumetric CT/MRI before it can be considered an appropriate surrogate measure.

Future directions

For health care professionals to be able to mitigate the adverse cardiometabolic effects that have been attributed to ADT, factors mediating this process need to be identified. Changes in body fat distribution, particularly gains in VAT are a plausible mechanism; however, given the limitations of studies to date, the effect of ADT on VAT remains to be elucidated. Longitudinal studies using tools capable of accurately assessing changes in abdominal adipose tissue (such as CT or MRI) are needed to delineate the effect of ADT on VAT and SAT and how this relates to cardiometabolic risk. Additionally, specific thresholds or reference limits of VAT volumes need to be identified that are clinically significant for stratifying those with differing levels of cardiometabolic or disease risk. This would be needed to support the use of monitoring changes in adipose tissue distribution in routine clinical practice. Notably, CT and MRI have limited clinical feasibility, and so newly developed methods of estimating VAT from a whole-body DXA scan may show promise for both researchers and clinicians to be able to quantify VAT in men undergoing ADT. However, further research

is needed to establish the accuracy of DXA compared to the gold standard volumetric CT/MRI among men undergoing ADT.

Furthermore, in recent years, there has been an increase in the use of alternatives or modifications to continuous ADT, including the use of intermittent ADT as first-line therapy for advanced PCa and the addition of secondary hormone therapies such as abiraterone and enzalutamide for castrate-resistant PCa. There has also been renewed interest in the use of parenteral estradiol as an alternative form of continuous ADT (Phillips *et al.* 2014). This is supported by results from studies such as the PATCH trial, in which it was reported that transdermal estradiol resulted in comparable levels of testosterone suppression and CVD event rates to GnRH agonists, while mitigating the bone loss seen with the GnRH agonist (Langley *et al.* 2008, 2013, 2016). However, the effect of these treatments on body fat distribution and cardiometabolic risk factors has received little attention, and given they are being increasingly used in clinical practice, this should also be an important focus of future research.

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