Screening for cardiovascular risk in patients with anorexia nervosa

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In young people, especially females, a high importance is placed on body image and physical appearance. Unfortunately, misperceptions of the ideal body shape and weight can encourage a pre-occupation with weight loss strategies. Long-term, these strategies may lead to ill-health due to inadequate caloric intake, use of pharmacological agents, and extreme weight control methods such as fasting and excessive exercise (Shisslak et al, 1995; Reinking and Alexander, 2005; Petrie et al, 2009) potentially leading to eating disorders such as anorexia nervosa. The following review focuses on appropriate screening techniques for identifying the risk of cardiovascular disease (CVD) in patients with this eating disorder.

Anorexia nervosa: Definitions, prevalence and prognosis

Anorexia nervosa (AN), according to the American Psychiatric Association (2000) and World Health Organization (1994), is diagnosed where there is evidence of low body weight and a refusal to maintain body weight within 85% of an age-predicted normal range accompanied by an extreme fear of 'fatness', a distorted body image and menstrual dysfunction (cessation of at least three consecutive menstrual cycles). The low body weight is the consequence of self-induced weight loss mediated through severe caloric intake restriction. Individuals present with a very low body weight, low percentage of body fat, energy deficiency and menstrual dysfunction.

Signs and symptoms of AN include excessive exercising with low body weight, blood in vomit, inadequate fluid intake in combination with poor eating, and rapid weight loss (Treasure, 2004). Change in body mass index (BMI) is often used as a surrogate marker of AN risk, however, the utility of BMI as a diagnostic marker is limited for a number of reasons and it is recommended that BMI measures should be combined with an examination of resting heart rate, blood pressure, peripheral circulation, core temperature and muscle strength using the stand up/squat test (Treasure, 2004). For further information on this topic interested readers should visit www.eatingresearch.com. In young people, a BMI below the second percentile is often a useful diagnostic threshold—further information is available at www.cdc.gov/growthcharts.

AN is a potentially life-threatening eating disorder with the highest rates for premature mortality of any psychiatric disorder in adults (Papadopoulos et al, 2009; Attia, 2010). In the UK, prevalence data is sparse but it is estimated 4 in 1000 females have AN, which equates to 1.4 million females (National Institute of Health and Clinical Excellence (NICE), 2004). However this figure is considered somewhat conservative as it is based on primary care referral data and many individuals with eating disorders may either not seek medical advice or seek advice through private medical units (NICE, 2004).

The prognosis for AN is poor with a six-fold increase in standard mortality rates compared with the general population (Papadopoulos et al, 2009). The longevity of the illness will also affect mortality risk. In the US, data collected by the Mayo Clinic between 1938 and 1984 indicate a mortality rate of 5% when the sufferer has been diagnosed with AN for between 4 and 5 years, however, in enduring AN of 20–30 years, risk of sudden cardiac death (SCD) increases alarmingly to 15–20% (Lucas et al, 1991).

ABSTRACT

In young people, especially females, a high importance is placed on body image and physical appearance. Unfortunately, misperceptions of the ideal body shape can encourage a pre-occupation with weight loss strategies. Long-term, these strategies may lead to ill-health—anorexia nervosa (AN) is a condition where there is evidence of low body weight, a refusal to maintain body weight, a distorted body image, and menstrual dysfunction. This review focuses on screening techniques for identifying cardiovascular risk in patients with AN.

Predictors of cardiac risk have not been robustly investigated in AN, consequently health professionals involved in cardiovascular risk screening may be reliant on screening methodologies that are based on anecdotal evidence. The current inability to accurately predict cardiac events and sudden cardiac death in chronically ill patients with enduring AN is a concern that requires greater national attention

KEY WORDS

- Eating disorder
- Cardiovascular risk
- Sudden cardiac death

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Cardiovascular abnormalities in AN

In female patients diagnosed with AN, cardiovascular abnormalities are common and the risk of SCD is increased compared with healthy females (Casiero and Frishman, 2006). The likelihood of cardiovascular problems depends on the severity and/or duration of energy restriction, the amount, rate, and composition of weight loss, and the degree of electrolyte imbalances (Beals, 2004).

Studies show that cardiac complications, including electrocardiographic (ECG) abnormalities, reduced ventricular mass, impaired myocardial performance, atrial and ventricular arrhythmias, myocardial infarction, pericardial effusion and mitral regurgitation, are evident in up to 86% of AN patients (Krantz et al, 2005; Myslobodsky, 2005; Olivares et al, 2005). In enduring AN, abnormal neuroendocrine responses also increase cardiovascular risk. Low levels of leptin and insulin, and elevated levels of ghrelin and possibly adiponectin have been observed (Misra and Klibanski, 2010) in conjunction with adverse lipid profiles (Friday et al, 1993; De Souza and Williams, 2004) and endothelial dysfunction (Zeni-Hoch et al, 20030; Ricklund et al, 2005). The negative physiological effects on the cardiovascular system are thought, partially, to be a result of hypothalamic hypoestrogenism (low oestrogen levels).

Rapid weight loss in patients with AN leads to a marked loss of skeletal muscle tissue, which is complicated by electrolyte imbalances often caused by habitual use of diuretics, emetics, and laxatives that can potentially lead to arrhythmias and ultimately SCD (Nudel et al, 1984). In AN, arrhythmias often manifest as acute bradycardia and may occur as a consequence of the body's attempt to conserve energy by reducing cardiac output (Vazquez et al, 2003). Several different pathological mechanisms have been proposed, including electrolyte loss, interstitial oedema, reduction in the glycogen content of the myocardium, and myofibrillar atrophy, which have been demonstrated in rat models (Clark and Wildenthal, 1986; Tolnai and von Althen, 1987).

Electrical and structural cardiac abnormalities in AN

The precise characterization of heart rate dynamics may have important clinical implications (Vigo et al, 2008). Many female AN patients will have significantly increased QT intervals compared with healthy females of the same age. The QT interval represents the time delay between the start of the Q wave and the end of the T wave and is known as the QTc interval when corrected for heart rate. QTc interval is often considered to be increased if it is

greater than 440 milliseconds (Vasquez et al, 2003).

The value of a prolonged QT dispersion (QTd) for predicting severe ventricular arrhythmias and SCD are well established (Swenne and Larsen, 1999). The QTd interval is the difference between the maximum and the minimum QTc intervals measured in the 12 leads, cut-off values around 60 milliseconds have been reported (Toivonen, 2002), and this marker may be used as a predictor of cardiovascular risk in patients with AN.

Furthermore, the measurement of heart rate variability (HRV) may also be useful in AN patients as increased QT interval variability is associated with serious cardiac arrhythmias in this population (Koschke et al, 2009). HRV reflects the variability in the time intervals between consecutive heart beats and indicates the balance in the autonomic nervous system as a consequence of sympathetic/parasympathetic activity. Ishizawa et al (2008) reported that 32 AN patients had reduced sympathetic responsiveness and increased parasympathetic responsiveness compared with 37 healthy controls following a period of rest in the supine position. HRV appears to be abnormal in AN patients compared with healthy controls (Kriepe et al, 1994; Petretta et al, 1997; Casu et al, 2002; Melanson et al, 2004).

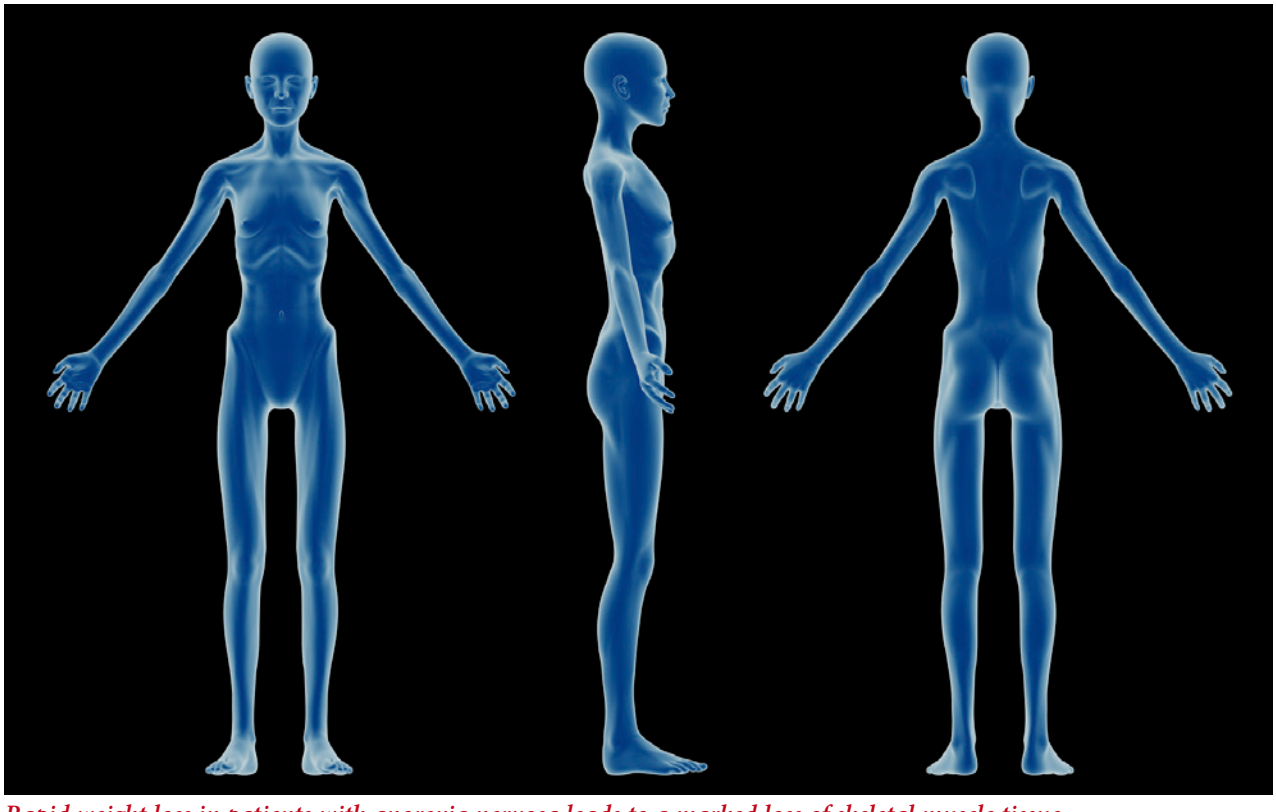
Structural cardiac abnormalities are also evident in AN patients as cardiac chamber size and left ventricular mass are reduced compared with healthy aged-matched controls, in absolute terms and after adjustment for body mass (Vazquez et al, 2003), which may relate to the consequences of longstanding hypovolemia (Casiero and Frishman, 2006). Consequently, cardiac output is reduced and peripheral vascular resistance increases despite the presence of hypotension.

Vazquez et al (2003) also suggested that the reduction in left ventricular mass may be responsible for the increase in QT interval dispersion in AN patients, which in turn may be explained by alterations in cardiac muscle fibres and in the function of potassium channels in the hypotrophied cardiac myocytes.

Cardiovascular risk factors in AN

Evaluation of traditional risk factors is an important first step in the identification of individuals with AN who are at risk of developing CVD. Novel blood biomarkers relevant to the pathophysiology of atherothrombosis—for example, inflammatory response markers, coagulation markers, platelet aggregation markers, and markers of lipoprotein or lipid-related variables—have been proposed in the assessment of atherosclerotic progression (Koenig, 2007). In addition, the development of non-invasive procedures to evaluate cardiovascular vessel structure and function is becoming increasingly important (Cohn et al, 2009).

However, we need to consider whether these contemporary risk factors are relevant to the AN population who are traditionally young with low body weight and have a low dietary fat intake. Hypothalamic amenorrhoea (HA), the consequence of severe caloric restriction and oestrogen deficiency, is a significant risk factor in patients with long-term AN, carrying a heavy burden of physical morbidity and cardiovascular mortality (Casiero and Frishman, 2006; Lawson et al, 2007; Attia, 2010). HA is a reversible disorder that results in cessation of the menses (Marcus et al, 2001).



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Rapid weight loss in patients with anorexia nervosa leads to a marked loss of skeletal muscle tissue

HA displays a strong interaction between psychological factors and endocrine function (Giles and Berga, 1993). Individuals with eating disorder symptoms, poor coping mechanisms, and mood disorders are all susceptible to HA. Studies have linked HA to impaired bone health and more recently to an altered cardiovascular phenotype, due to adaptations in vascular function and autonomic regulation (Zeni-Hoch et al, 2003; O'Donnell et al, 2009).

Given the established link between low left ventricular ejection fraction (LVEF) and subsequent SCD in cardiac populations, echocardiographic measurements may also be important for risk prediction in the AN population (Shiga et al, 2009). It has been suggested that echocardiographic assessment of cardiac structure and function and serum electrolyte measurements may enhance the prognostic outcome of HRV studies (Vigo et al, 2008). Echocardiography and the biomarker B-type natriuretic peptide (BNP) appear to provide a powerful incremental assessment of cardiac function, clinical status, and outcome across the spectrum of cardiac disease and there is strong evidence to support their integrated use in the diagnosis and management of cardiovascular disease (Misra et al, 2004; Troughton and Richards, 2009). However, supportive evidence is sparse in the AN population and more research is required, which may allow a more targeted screening algorithm to be developed.

The use of novel serum biomarkers that are predictive of premature CVD risk may also be important in AN patients. The ideal risk marker would be one that provides detailed and reliable prognostic information with sufficient sensitivity and specificity to direct specific interventions that improve outcomes, while remaining inexpensive, simple to interpret, safe to obtain and readily accessible in a broad range of health-care environments (Rosenbaum, 2008). Clearly further research is required to develop effective and inexpensive biomarkers for assessing CVD risk in AN.

As a consequence of a long-term loss of lean tissue, patients with enduring AN will lose oestrogen and therefore the regularity of the menstrual cycle is affected (Leung et al, 2004). Despite the prescription of oral oestrogen to offset the risk of amenorrhea, cardiovascular risk remains elevated as oral oestrogen adversely raises levels of high-sensitivity C-reactive protein (hs-CRP), a potent inflammatory risk marker for CVD (Leung et al, 2004; Lawson, et al, 2007). Lawson and colleagues (2007) reported that in females with AN who were prescribed oestrogen-based oral contraceptive pills, there was a greater than 20% likelihood of having higher risk hs-CRP levels (>3 mg/litre). The authors suggested that the accompanying raised interleukin-6 (IL-6) response in these participants may indicate an increased systemic inflammatory influence on hs-CRP levels. This observation raises the possibility that elevated hs-CRP levels in young females with AN could be predictive of future cardiac events, particularly if a higher than normal hs-CRP level is chronically sustained.

Screening AN patients for CVD risk has traditionally focused on physical/physiological factors. However, some psychological conditions also carry a CVD risk burden. Depression and anxiety have previously been associated with increased cardiac morbidity and mortality in clinical and healthy populations (Barth et al, 2004; Frasure-Smith and Lespé, 2008). Further, links between an elevated risk for cardiac events and the 'distressed' type-D personality, characterized by negative affectivity and social inhibition, have been made.

Table 1.
Current CVD risk algorithm in patients with anorexia nervosa

Investigation	Threshold of consideration	Threshold of action
Body mass index (kg/m^2)	<14	<12
Weight loss/week (kg)	>0.5	>1.0
Temperature °C	<35	<34.5
Blood pressure (mmHg)	<90/<70	<80/<60
Heart rate (bpm)	<50	<40
Haemoglobin (g/dl)	<11.0	<9.0
Potassium (mmol/litre)	<3.5	<3.0
Sodium (mmol/litre)	<135	<130
Urea (mmol/litre)	>7	>10
Corrected QT interval (QTc; milliseconds)		>450*

*Note that ECG is recommended in all AN patients if BMI is <14 kg/m^2 and if drugs that may effect ECG trace are prescribed

If a patient's health status falls into the 'threshold of consideration' then weekly reviews of his/her status are recommended, which may include urgent referral to an eating disorders specialist. If a patient's health status falls into the 'threshold of action' then immediate contact and referral to an eating disorders clinic is necessary. Urgent medical attention is required

Adapted from Treasure 2004

Denollet (2005) suggested that an examination of acute (such as current stress) and long-term (such as type-D personality) psychological factors may be useful in identifying high-risk candidates for cardiac events or SCD. It has been speculated that elevated cortisol (a stress hormone) may be the mediating factor in the association between type-D personality and an increased risk of CVD (Sher, 2005) although further research is required. It is possible that there is a higher prevalence of type-D personality in AN patients, however, further research is required to confirm this assertion.

Routine screening investigations

In order to identify the severity of CVD risk in AN patients a screening pathway was proposed by Treasure (2004). For the purposes of this article we have adapted the content to focus specifically on CVD risk (*Table 1*), however, the original paper focused on global medical risk in AN patients. We would suggest that this should be used as a good starting point and propose that further research be undertaken that is focused on optimizing the screening protocol for CVD risk in AN patients.

Conclusions

Predictors of cardiac risk have not been robustly investigated in AN, consequently health professionals involved in CV risk screening and prevention may be reliant on screening methodologies that are based on anecdotal evidence. It is not surprising that in primary care, SCD detection rates in AN patients is low. The current inability to accurately predict cardiac events and SCD in chronically ill patients with AN is a concern that requires greater national attention.

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Key Points

- Anorexia nervosa (AN) is a condition where there is evidence of low body weight, a refusal to maintain body weight, an extreme fear of 'fatness', and a distorted body image, and menstrual dysfunction
- AN is a potentially life-threatening eating disorder with the highest rates for premature mortality of any psychiatric disorder in adults
- In the UK, prevalence data is conservatively estimated to be 4 per 1000 females which equates to around 1.4 million females
- The prognosis for AN is poor with a six-fold increase in the standard mortality rates compared with the general population
- Poor prognosis is strongly associated with increased cardiac risk in AN patients
- More robust screening modalities for identifying CV risk are required to assist health professionals involved in cardiovascular risk screening and prevention in early detection, diagnosis and management of sudden cardiac death risk in AN