Cardiovascular Diseases and Metabolic Syndrome

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55.1 Introduction

Cardiovascular disease (CVD) is a broad term covering disorders of the heart and blood vessels and includes hypertension, coronary heart disease, cerebrovascular disease, peripheral vascular disease, heart failure, rheumatic heart disease, congenital heart disease and cardiomyopathies (WHO 2017).

CVD is common; the World Health Organisation (WHO) estimates that more than 17.5 million people died of CVD such as heart attack or stroke in 2012, representing 30% of all global deaths. CVDs are the number one cause of death globally: more people die annually from CVDs than from any other cause. It is predicted that by 2030, almost 23.6 million people will die from CVDs, mainly from heart disease and stroke. These are projected to remain the single leading causes of death (WHO 2017).

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After HSCT, there is an increased incidence of CVD. Retrospective EBMT analyses have shown the cumulative incidence of a first cardiovascular event 15 years after HSCT rises to 6%. The type of transplant may be important. In the EBMT analyses, the cumulative incidence of 7.5% for the first CV event at 15 years post allo-HSCT versus 2.3% post auto-HSCT (Tichelli et al. 2007). However, in another study with a 7 year median follow-up (range 2–23.7) the 10 year cumulative incidence of ischaemic heart disease (IHD), cardiomyopathy, stroke and all-cause CV death was 3.8%, 6%, 3.5% and 3.7% respectively with similar prevalence in auto- and allo-HSCT (Chow et al. 2011).

55.2 Risk Factors

A number of pre-transplant risk factors appear to predispose to CVD (such as smoking, hypertension, dyslipidaemia, diabetes and obesity). CV toxicity of pre-transplant treatment includes anthracyclines and site-specific radiotherapy.

CV toxicity of transplant includes GVHD, and CV toxicity of post transplant treatment includes corticosteroid use and retransplant. Other contributing risk factors emerge as secondary late effects, such as hypogonadism, premature menopause and hypothyroidism (Chow et al. 2014).

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When risk factors combine; the term *metabolic syndrome (MetS)* is used. MetS is a cluster of interrelated factors which increase the risk of cardiovascular disease, diabetes mellitus (DM) and all-cause mortality (Alberti et al. 2009; NCEP 2002).

55.3 Metabolic Syndrome Definition

The existence of several definitions of MetS led to a harmonised definition (IDF 2006): that is, the presence of three out of five risk factors as follows:

- Abdominal obesity measured by waist circumference: With population and country specific definitions.
- Triglycerides ≥1.7 mmol/L or drug treatment for elevated levels.
- HDL-C (men) <1.0 mmol/L or drug treatment for reduced levels.
- HDL-C (women) <1.3 mmol/L or drug treatment for reduced levels.
- Blood pressure ≥130/≥85 mmHg or drug treatment for hypertension (HTN).
- Fasting glucose ≥5.6 mmol/L drug treatment for diabetes mellitus (DM).

The International Diabetes Foundation (IDF) estimates 25% of the world's population has MetS (IDF 2006).

After HSCT there is an increased incidence of MetS, with reported prevalence rates of 31–49% (Majhail et al. 2009b; McMillen et al. 2014; Oudin et al. 2015; Greenfield et al 2018). In HSCT patients, the increased incidence is accounted for by the following components:

55.3.1 Abdominal Obesity

Abdominal obesity measured by waist circumference represents fat accumulation (visceral adipose deposits) which independently confers cardiometabolic risk (Amato et al. 2013). Changes in waist circumferences are seen after HSCT with, for example, corticosteroid use and with onset of sarcopenic obesity.

55.3.2 Dyslipidaemia

Dyslipidaemia is defined by elevated levels of total cholesterol, LDL-C or triglycerides or low levels of HDL-C. Prevalence in general population is estimated at 25% in the USA (Baker et al. 2007) and in European countries (Fodor 2010; Scheidt-Nave et al. 2013; Gonzalez-Juanatey et al. 2011). Evidence suggests allo-HSCT recipients have significantly higher risk of new onset dyslipidaemia (RR2.1 CI 1.1504.65) compared with auto-HSCT (Tichelli et al. 2007) with the prevalence post HSCT estimated to be 43–73% (FACT-JACIE 2017). Factors predicting dyslipidaemia after HSCT include family history, obesity, high dose total body irradiation, grade II–IV aGvHD, cGvHD, CLD and IST use (Chow et al. 2014; Oudin et al. 2015; Kagoya et al. 2012; Blaser et al. 2012).

55.3.3 Hypertension (HTN)

Hypertension (HTN) in the general population is defined as systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg but defined in context of MetS as systolic BP ≥135 mmHg or diastolic BP ≥85. HTN in people following allo-HSCT is 2.06 times (95% CI 1.39–3.04) more likely compared with sibling donors or auto-HSCT (Baker et al. 2007).

55.3.4 Insulin Resistance or Diabetes Mellitus (IR/DM)

DM is characterised by hyperglycaemia resulting from defects in insulin secretion, insulin action or both and defined as a fasting pGL ≥7 mmol/L, an HbA1C ≥6.5%, a 2 h plasma glucose ≥11.1 mmol/L during a glucose tolerance test (GTT) or a random glucose ≥11.1 mmol/L.

Both allo-HSCT and auto-HSCT recipients have been found to report DM more often than

sibling donors (OR for allo-HSCT, 3.65; 95% CI, 1.82–7.32; OR for auto-HSCT: 2.03; 95% CI, 0.98–4.21) (Baker et al. 2007). High-dose corticosteroids (cumulative PRD dose of >0.25 mg/kg/day) increase the likelihood of developing DM (RR, 3.6; 95% CI, 1.7–7.5) and for having persistent DM at 2 years post-HSCT (RR, 4.1; 95% CI, 1.0–18.2) (Majhail et al. 2009a; b). TBI is also a well-evidenced risk factor (Hirabayashi et al. 2014).

55.4 Preventative Practices in the HSCT and Late Effects Clinic: A Practical Approach

Clearly HSCT clinicians cannot be expected to manage all cardiovascular risk factors and complications. The logistics would be overwhelming and the clinical expertise required to provide up-to-date management of cardiological, cerebrovascular, endocrinological and metabolic conditions lacking.

However, the fact that HSCT survivors require HSCT follow-up provides an opportunity to deliver screening for late effects and other long-term consequences of treatments. Screening for cardiovascular risk factors, including MetS and CV events, can be straightforwardly integrated into a programme of long-term and late effects follow-up.

Screening can be provided by a variety of clinicians, medical, nursing or other allied professions, depending on the model of care. If cardiovascular risk factors are detected, given the commonality, they can usually be referred back to primary care clinicians who are more experienced and frequently manage a range of long-term conditions including hypertension, glycaemic control and often have access to weight management, smoking cessation and similar relevant serves. Primary care clinicians are familiar with using risk assessment algorithms, such as the Framingham risk score (Framingham 2008) and many others which are country specific. These risk assessment tools may be useful in estimating a person's projected risk of developing CVD in the general population. They have limitations (age ethnicity, comorbid conditions) and, importantly, have not been validated in HSCT survivors and may potentially under-estimate the risk. However, it is reasonable for primary care and other clinicians to apply them until some more specific instrument is developed in HSCT survivors.

Non-acute cardiovascular problems detected in the late effects clinic can be referred back to primary care clinicians who can manage them or refer on for specialist treatment. However, there should be direct referral for clinically urgent or more serious cardiovascular problems to relevant hospital specialists, who have a state-of-the art knowledge and experience in a rapidly evolving field. Ultimately, one indispensable aspect should be close communication between all clinicians involved in the short- and long-term management of the HSCT patient, whether at primary, secondary or tertiary levels of care.

Given the specialised complexity of HSCT and its many complications, which are relatively rarely encountered by many clinicians outside of haematology, oncology and immunology, the HSCT clinic and associated late effects service can have a major role in coordinating care and facilitating communication between other relevant specialists. This aspect in underpinned by the seventh edition of the FACT-JACIE standards which feature systematic provision for late effects follow-up, including cardiovascular risk factors and complications (FACT-JACIE 2017).

For the HSCT programme and/or associated late effects clinic, Table 55.1 has been published as a guide to facilitate screening in the EBMT-CIBMTR guidelines (DeFilipp et al. 2017). This is a consensus opinion, and there is no good evidence of the safety or clinical effectiveness of these recommendations in HSCT patients, which are based on the general population. Based on the available evidence, it is important to screen for other factors in HSCT patients, including (a) personal history, (b) family history, (c) type of transplant (allo or auto), (d) use of TBI, (e) history of acute or chronic GvHD and (f) use of CNI (CSA, TAC) (DeFilipp et al. 2017).

Table 55.1 Screening guidelines for metabolic syndrome and cardiovascular risk factors for adult and paediatric patients among the general population and HSCT survivors. Taken from DeFilipp et al. 2017

	General adult population (http://www.uspreventiveservicestaskforce.org/)	Adult long-term HCT survivors Majhall et al. (2012)	General pediatric population (http://www.nhlbi.nih.gov)	Pediatric long-term HCT survivors Pulsipher et al. (2012)
Weight, height and BMI	Weight, height and BMI assessment in all adults (no specific recommendation for screening interval)	No specific recommendations	Weight, height and BMI assessment after 2 years of age (no specified screening interval)	Weight, height and BMI assessment yearly
Dyslipidemia	For persons with increased risk for coronary heart disease, assessments should begin at age 20	Lipid profile assessment every 5 years in males aged ≥35 years and females aged ≥45 years	Lipid panel between 9 and 11 years of age or earlier if family history	Lipid profile at least every 5 years; if abnormal, screen annually
	The interval for screening should be shorter for people who have lipid levels close to those warranting therapy, and longer intervals for those not at increased risk who have had repeatedly normal lipid levels	Screening should start at age 20 for anyone at increased risk (smokers, DM, HTN, BMI ≥30 kg/m^2 and family history of heart disease before age 50 for male relatives or before age 60 for female relatives)		
Blood pressure	Blood pressure assessment every 3–5 years in adults aged 18–39 years with normal blood pressure (<130/85 mmHg) who do not have other risk factors	Blood pressure assessment at least every 2 years	Blood pressure assessment yearly after the age of 3 years, interpreted for age/sex/height	Blood pressure assessment at each visit and at least annually
	Blood pressure assessment annually in adults aged ≥40 years and for those who are at increased risk for high blood pressure (blood pressure 130 to 139/85 to 89 mmHg, those who are overweight or obese, and African–Americans)			
Hyperglycemia	Screening for abnormal blood glucose (HbA1C, fasting plasma glucose or oral glucose tolerance test) every 3 years in adults aged 40–70 years who are overweight or obese.	Screening for type 2 DM every 3 years in adults aged ≥45 years or in those with sustained higher blood pressure (>135/80 mmHg)	Fasting glucose every 2 years after the age of 10 years in overweight children with other risk factors	Fasting glucose at least every 5 years; if abnormal, screen annually

Abbreviations: *BMI* body mass index, *DM* diabetes mellitus, *HbA1C* hemoglobin A1C, *HCT* hematopoietic cell transplantation, *HTN* hyper tension

55.5 Future Directions: Implementation, Education and Research

As survival after HSCT gradually increases, there is recognition of an impact on CVD and its risk factors, including MetS. Most research has been cross-sectional and observational. More prospective research is needed on both defining the incidence above the normal ageing population and on interventional strategies, targeting individual risk factors and/or components of the MetS. Indeed, a recent review by Armenian and colleagues (Armenian et al. 2017) provided consensus recommendations for cardiovascular disease and risk factors identifying research gaps and future study priorities to improve the long-term cardiovascular health of HSCT survivors.

Consideration of CVD and associated risk factors may also vary between indications for HSCT. For example, the most common indication for HSCT, myeloma, although mostly incurable, is now associated with relative longevity, and consideration of CV risks are relevant (Snowden et al. 2017). Likewise, new indications for HSCT, such as systemic AID, and newer techniques, such as haplo-HSCT, require individualised assessment. Whilst pharmacological, lifestyle and rehabilitation interventions are common in the general population in respect to CVD, their impact in HSCT recipients (both before and after HSCT) needs to be defined in the context of the wide range of indications and age at which patients receive their HSCT, along with the individual prognosis of each indication after successful HSCT.

Key Points

- Until more evidence is available, the best approach is to screen all patients (i.e. both autologous and allogeneic HSCT) according to international consensus guidelines (DeFilipp et al. 2017) and manage risk factors on an individual basis.
- The challenge of universal implementation of screening and management of late effects across various health services providing HSCT will be facilitated by FACT-JACIE accreditation standards.
- Systematic programmes of education and research for the development and validation of HSCT-specific care models are warranted (Battiwalla et al. 2017).

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