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Review

The need for re-defining cut-off values in heart failure: From obesity to iron deficiency

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ABSTRACT

The health status of older people is frequently complicated by one or more chronic diseases. Some conditions might have a different meaning in certain groups of elderly subjects, like in frail people or older patients with heart failure. Cut-off values defining these conditions may require adjustment in such groups. Indeed, several such conditions (e.g. obesity and hypercholesterolemia) have been discussed recently in light of so-called paradoxical situations, which are - counter-intuitively - associated with better outcome instead of a negative impact on survival in the general population. Therefore, different cut-off values may be needed in some groups of older subjects. The pathophysiological mechanisms for these paradoxical situations need to be understood in at least two different ways, causal and non-causal. The aim of this review is to provide an overview of a variety of conditions (obesity, dyslipidaemia, hypertension, and diabetes) in which new cut-offs may have diagnostic, clinical, or prognostic value, focusing on heart failure as a chronic disease, which is frequently observed in older patients. Haemoglobin concentration may need a different cut-off in heart failure for a reason other than paradox. Namely, underlying iron deficiency itself, both in those with or without anaemia, can have effects on symptoms and quality of life. Further studies will be needed for re-defining cut-off values in heart failure and maybe in the other chronic illnesses.

Contents

1. Introduction

Aging is associated with an increased prevalence of disease. Therefore, multimorbidity is present in many people aged 65 years and above (Barnett et al., 2012). Some conditions might have a different

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meaning in groups of older people, like in frail people or in older patients with heart failure (HF). In these groups, cut-off values for risk stratification or for the target of treatment may be different from those in the general population. Some of these conditions even represent so-called paradoxical situations. Paradox, otherwise termed reverse epidemiology, is a term used under conditions that are deemed to negatively impact survival in the general population but that may, counterintuitively, be associated with improved prognosis in certain groups of people, such as older individuals or those with chronic diseases. The obesity paradox and the cholesterol paradox are the most frequently discussed paradoxons in this regard and have been reported in detail before (Table 1). As can be seen in Table 1, paradoxons are observed for several conditions and co-morbidities that are observed in patients with HF. This review discusses several such conditions (obesity, dyslipidaemia, hypertension, diabetes, and anaemia) where new cut-offs might be helpful, including several types of paradoxical and other situations, by referring to previous studies which encompasses this topic with epidemiological, clinical, and physiological data. As an example of a chronic disease frequently complicated in older individuals, we focused on patients with HF due to the abundance of data from clinical studies. Paradoxical situations discussed in this review include the obesity paradox, the cholesterol paradox, and paradoxical situations with regards to blood pressure and haemoglobin A1c levels. Even though anaemia (haemoglobin levels) and the presence of iron deficiency do not represent such paradoxical situations, both are still addressed here due to their potential need to define alternative cut-offs for them.

Table 1
Paradox in chronic diseases.

Measured biomarkers	Chronic diseases	References
Body mass index (obesity paradox)	Heart failure	Davos et al. (2003), Horwich et al. (2001), Guder et al. (2009), Lavie et al. (2013), Lavie et al. (2014), Vest et al. (2015)
	Cardiovascular diseases (non-heart failure) (Coronary artery disease, atrial fibrillation, peripheral artery disease, stroke, venous thromboembolism)	Doehner et al. (2015), Lavie et al. (2009)
	Non-cardiovascular diseases (Chronic obstructive pulmonary disease, chronic kidney disease, rheumatoid arthritis, type 2 diabetes, hypertension)	Hainer and Aldhoon-Hainerova (2013) Ahmadi et al. (2015)
	Older population	Ahmadi et al. (2015)
Cholesterol (cholesterol paradox)	Heart failure	Afsarmanesh et al. (2006), Iwaoka et al. (2007), Rauchhaus et al. (2003), Velavan et al. (2007)
	Non-cardiovascular diseases (Chronic obstructive pulmonary disease, chronic kidney disease, rheumatoid arthritis)	Ahmadi et al. (2015)
	Older population	Ahmadi et al. (2015)
Blood pressure	Heart failure	Raphael et al. (2009)
	Chronic kidney disease	Kalantar-Zadeh et al. (2003)
	Older population	Ahmadi et al. (2015)
Blood glucose/hemoglobin A1c	Heart failure	Eshaghian et al. (2006), Aguilar et al. (2009)

2. Paradoxical situations

2.1. Obesity paradox

The obesity paradox means that higher body mass index (BMI) including overweight (a BMI of 25.0 to 29.9 kg/m^2) and obesity (a BMI >30.0 kg/m^2), which is associated with elevated risk of cardiovascular diseases and increased all-cause mortality in general population (Jensen et al., 2014), is counterintuitively associated with better outcome in certain groups of patients with chronic disease and in older people. The obesity paradox has attracted increasing attention in recent years (Lainscak et al., 2012). Its first description goes back to a publication dating back to 1999, when Fleischmann et al. studied hospitalisation rates and mortality in 1346 patients undergoing maintenance haemodialysis (Fleischmann et al., 1999). While it was expected that the underweight cohort would have lower survival, it came as a surprise that overweight and obese participants had a significantly higher survival rate than those with normal weight after one year of follow-up. Meanwhile, the obesity paradox has been implicated in a broad spectrum of chronic diseases such as chronic kidney disease, chronic obstructive pulmonary disease, cardiovascular diseases (including HF, coronary artery disease, atrial fibrillation, cardiac surgery, percutaneous coronary intervention, and stroke), each of them being often observed in older people (Table 1) (Doehner et al., 2015; Lainscak et al., 2012). These results suggest that the meaning of overweight and obesity is different in healthy individuals and older people with and without chronic diseases.

2.1.1. Obesity paradox in patients with heart failure

In patients with HF, obesity has an important role in the aetiology of the illness itself. On the other hand, advanced stages of HF are often associated with involuntary weight loss, known as cardiac cachexia (von Haehling and Anker, 2014). It has been shown that approximately 10% of all patients with HF are affected by cachexia. In addition, cardiac cachexia has been associated with poor outcome in HF (Anker et al., 1997). Based on these bidirectional mechanisms, many reports have been published regarding the association of BMI and outcomes in HF. Two epidemiological studies by Davos et al. and Horwich et al. have shown that patients with HF and a BMI of 29.2 $\pm$ 0.8 and 27.8 to 31.0 kg/m^2, respectively, showed the highest survival among 525 and 1203 HF patients (Davos et al., 2003; Horwich et al., 2001). Such paradox was observed irrespective of reduced or preserved ejection fraction (Guder et al., 2009). According to these studies, the upper limit of overweight (BMI of 25.0 to 29.9 kg/m^2) may be useful to be set as an alternative cut-off in affected patients. Several lines of thought have been suggested to explain the obesity paradox: one may be described as "causal", the other as "non-causal" (Table 2). The causal explanation embraces a hypothesis that suggests that obesity can protect patients with HF. The non-causal explanation implies that the obesity paradox is observed just as a result of chance (random error) or bias and confounding (Delgado-Rodriguez and Llorca, 2004). An example of a bias by unmeasured factors is collider stratification bias (Lajous et al., 2015; Perrone-Filardi et al., 2015) whereby patients with HF and obesity represent a selected subset of patients in whom other confounding risk factors for worse outcome (e.g. genes, lifestyle) are less pronounced. The other example includes lead time bias or misclassification bias (Wang, 2014). This type of bias by unmeasured factors has been ruled out using newer datasets that included several of the accused factors. Beneficial effects of muscle or even fat mass have been included in the causal pathophysiology with better outcomes in obese patients with HF. In other words, obese HF patients might have a better prognosis than non-obese patients because they have more muscle (and more fat), and this type of body composition may confer a beneficial effect. As better cardiorespiratory fitness, a consequence of high muscular strength, is a strong predictor of prognosis in HF, the obesity paradox may also be attributed to better cardiorespiratory fitness in obese