International Journal of Cardiology 171 (2014) 49–55

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

The obesity paradox in men with coronary heart disease and heart failure: The role of muscle mass and leptin ☆☆,★

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ARTICLE INFO

Article history:
Received 17 May 2013
Received in revised form 13 September 2013
Accepted 17 November 2013
Available online 23 November 2013

Keywords:
Obesity
Mortality
Cardiovascular disease
Leptin
Heart failure

ABSTRACT

Aims: We have investigated the role of muscle mass, natriuretic peptides and adipokines in explaining the obesity paradox.
Background: The obesity paradox relates to the association between obesity and increased survival in patients with coronary heart disease (CHD) or heart failure (HF).
Methods: Prospective study of 4046 men aged 60–79 years followed up for a mean period of 11 years, during which 1340 deaths occurred. The men were divided according to the presence of doctor diagnosed CHD and HF: (i) no CHD or HF ii), with CHD (no HF) and (iii) with HF.
Results: Overweight (BMI 25–9.9 kg/m^2) and obesity (BMI ≥ 30 kg/m^2) were associated with lower mortality risk compared to men with normal weight (BMI 18.5–24.9 kg/m^2) in those with CHD [hazards ratio (HR) 0.71 (0.56,0.91) and 0.77 (0.57,1.04); $p = 0.04$ for trend] and in those with HF [HR 0.57 (0.28,1.16) and 0.41 (0.16,1.09; $p = 0.04$ for trend). Adjustment for muscle mass and NT-proBNP attenuated the inverse association in those with CHD (no HF) [HR 0.78 (0.61,1.01) and 0.96 (0.68,1.36) $p = 0.60$ for trend) but made minor differences to those with HF [$p = 0.05$]. Leptin related positively to mortality in men without HF but inversely to mortality in those with HF; adjustment for leptin abolished the BMI mortality association in men with HF [HR 0.82 (0.31,2.20) and 0.99 (0.27,3.71); $p = 0.98$ for trend].
Conclusion: The lower mortality risk associated with excess weight in men with CHD without HF may be due to higher muscle mass. In men with HF, leptin (possibly reflecting cachexia) explain the inverse association.

1. Introduction

Despite the well-established adverse association between obesity and risk of developing cardiovascular disease and heart failure (HF), a large body of evidence indicates that overweight and obesity are associated with increased survival in patients with HF [1–3] an unexpected finding commonly termed the 'obesity paradox'. Numerous investigators and meta-analysis of studies in cohorts with coronary heart disease (CHD) have also demonstrated this paradoxical relationship in patients with CHD [4–8] although this has not been seen in all studies after adjustment for confounders [9,10]. The aetiology of this paradoxical association remains largely unexplained but a number of explanations have been proposed [4,11,12]. BMI is a poor marker of body fat and does not distinguish between fat and lean body mass which has been associated with increased mortality [13]. Abdominal obesity has been suggested as a better marker of obesity risk. Indeed, meta-analysis of cohorts in CHD has shown positive associations between WC and mortality [14]. In HF, the obesity paradox may be driven by the deleterious effects of cachexia (i.e. weight loss) reflecting the combined loss of muscle and adipose tissues [15]. It has also been postulated that several physiologic mechanisms may explain the protective effect of a higher BMI on mortality [12]. NT-proBNP levels are lower in overweight and obese patients; lower NT-proBNP predicts lower mortality [12,16]. Another possible

Abbreviations: NT-proBNP, N-terminal pro-brain natriuretic peptide; HF, Heart failure; MI, Myocardial infarction; CHD, Coronary heart disease; CRP, C-reactive protein; WC, Waist circumference; BMI, Body mass index; MAMC, Mid arm muscle circumference.

☆☆ Funding sources: The British Regional Heart Study is a British Heart Foundation (BHF) research group and receives support from the BHF Programme grant (RG/08/013/25942).
★ Disclosure: None.
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0167-5273
http://dx.doi.org/10.1016/j.ijcard.2013.11.043

explanation for the obesity paradox directly involves the functions of adipose tissue [12,15]. Adipose tissue produces leptin which experimental studies suggest may have protective effects in HF [17] and adiponectin is decreased in obesity; lower concentrations of adiponectin have been associated with lower mortality in patients with CHD or HF [18–20]. However few population studies to date have examined the possible role of lean muscle mass, adipokines (leptin, adiponectin) and NT-proBNP in explaining the obesity paradox, although previous studies suggest that NT-proBNP and adiponectin may explain the obesity paradox in HF [18,21]. In a previous report, we observed a positive association between BMI and mortality in older adults without HF once muscle mass had been taken into account [13]. However, the association of BMI and mortality in men with CHD or HF has not been specifically examined. We have examined the association between BMI and all-cause mortality separately in men with diagnosed CHD without HF and in men with HF (with or without CHD) and examined the role of muscle mass, adipocytes and NT-proBNP in explaining the obesity mortality paradox in these two groups. To see whether the obesity paradox is specific to those with established CHD or HF the association between BMI and mortality is also presented in those without CHD or HF.

2. Subjects and methods

The British Regional Heart Study is a prospective study of cardiovascular disease involving 7735 men aged 40–59 years selected from the age–sex registers of one general practice in each of 24 British towns, who were screened between 1978 and 1980 [22]. In 1998–2000, all surviving men, now aged 60–79 years, were invited for a 20th year follow-up examination. Ethical approval was provided by all relevant local research ethics committees. All men provided informed written consent to the investigation, which was carried out in accordance with the Declaration of Helsinki. All men completed a mailed questionnaire providing information on their lifestyle and medical history, had a physical examination and provided a fasting blood sample. The samples were frozen and stored at −20 °C on the day of collection and transferred in batches for storage at −70 °C until analysis, carried out after no more than one freeze–thaw cycle. 4252 men (77% of survivors) attended for examination. 12 lead electrocardiograms were recorded using a Siemens Sicard 460 instrument and were analyzed and coded in accordance with Minnesota Coding definitions at the University of Glasgow ECG core laboratory based at Glasgow Royal Infirmary [23].

2.1. Anthropometric measurements

Measurements at re-examination (1998–2000) included height, weight, waist circumference, triceps skinfold thickness and mid-upper arm circumference (MUAC). The waist measurement was taken from the midpoint between the iliac crest and the lower ribs measured at the sides. Body mass index (BMI; weight/height^2 in kg/m^2) was calculated for each man. Mid arm muscle circumference (MAMC) was calculated as MUAC − 0.3142*(triceps skinfold thickness) [24]. MAMC were considered an indicator of muscle mass. MAMC has been shown to correlate strongly with more accurate dual-energy X-ray absorptiometry (DXA) measures of lean body mass [25]. Men with BMI <18.5 and those with missing data on MAMC were excluded (n = 32).

2.2. Cardiovascular risk factors and mobility limitation

Details of measurement and classification methods for smoking status, physical activity, social class, alcohol intake, blood pressure, blood lipids and lung function (forced expiratory volume in one second [FEV_1] in this cohort have been described [13,26]. Predicted glomerular filtration rate (eGFR) (renal function) was estimated from serum creatinine using the Modification of Diet in Renal Disease equation; eGFR = 186 × creatinine − 1.154 × age − 0.203. C-reactive protein (CRP) was assayed by ultrasensitive nephelometry (Dade Behring, Milton Keynes, UK). Prevalent diabetes included men with diagnosed diabetes or men with fasting blood glucose ≥7 mmol/l. The men were asked whether they currently had difficulty carrying out any of the four following activities on their own as a result of a long term health problem: (i) going up or down stairs, (ii) bending down or straightening up, (iv) keeping one's balance and (iv) walking for a quarter of a mile on the level. Mobility limitation was defined as men reporting difficulty in any one of the above [27].

2.3. Adiponectin, leptin and NT-proBNP

Plasma adiponectin concentrations were determined using ELISA (R&D systems, UK). The intra-assay and the inter-assay coefficients of variability were each 7.5%. We have previously shown this method to correlate well with a radioimmunoassay method for adiponectin measurement [20]. Plasma leptin was measured by an 'in house' radioimmunoassay carefully validated against the commercially available Linco assay, as previously described [28]. The intra- and inter- assay coefficients of variation were <7% and <10%, respectively, over the sample concentration range. The detection limit of the assay was 0.5 ng/ml which is superior to commercial assays. NT-proBNP was determined using the Elecsys 2010 electrochemiluminescence method (Roche Diagnostics, Burgess Hill, UK). Samples were snap-thawed at 37 °C and assayed on the analyzer, which was calibrated using the manufacturer's reagents. Manufacturer's controls were used to monitor assay drift, using both a high and low control, with limits of acceptability defined by the manufacturer. Low control CV was 6.7% and high control CV was 4.9% [29].

2.4. Follow-up

All men have been followed up from initial examination (1978–1980) for cardiovascular morbidity and mortality [30] and follow-up has been achieved for 99% of the cohort. In the present analyses, all-cause mortality is based on follow-up from re-screening in 1998–2000 at mean age 60–79 years to June 2010, a mean follow-up period of 11 years (range 10–12 years). Information on death was collected through the established "tagging" procedures provided by the National Health Service registers. A non-fatal myocardial infarction (MI) was diagnosed according to World Health Organisation criteria. Evidence of non-fatal MI and HF was obtained by ad hoc reports from general practitioners supplemented by biennial reviews of the patients' practice records (including hospital and clinic correspondence) and from repeated personal questionnaires to surviving subjects after initial examination through to the end of the study period. Incident non-fatal HF was based on a doctor diagnosis of HF from primary care records and confirmed by a clinical record review by the Research Team.

2.5. Men with CHD and HF

The men were asked whether a doctor had ever told them that they had angina or MI, HF, stroke, diabetes and a number of other CVD conditions. Patient recall of a doctor diagnosis of CHD has been shown to be a valid measure of recording diseases in this study population [31,32]. The kappa statistics comparing record review with patient's recall of CHD was 0.82 [31]. On the basis of recall of doctor diagnosis of CHD (MI, angina, coronary revascularisation) and ECG evidence of definite MI in 1998–2000 and regular surveillance of general practitioner's records of major non-fatal MI, or HF occurring before that point, the men were divided into three groups based on their CHD and HF status:

(i) Men without CHD or HF (n = 3174) as defined in (ii) and (iii) below.
(ii) Those with prevalent diagnosed CHD or ECG evidence of definite MI but no diagnosed HF (N = 860).
(iii) Those with doctor diagnosed HF (with or without CHD) confirmed in the primary care records and confirmed by a review of the clinical features of diagnosed HF cases (symptoms, signs, treatment response) by the Research team to ensure they are consistent with European Society of Cardiology recommendations on diagnosis [33] (n = 86).

2.6. Statistical methods

The distributions of leptin, adiponectin and NT-proBNP were skewed and log transformation was used. Cox's proportional hazards model was used to assess the multivariate-adjusted hazards ratio. Overweight (25–29.9 kg/m^2) and obesity (≥30 kg/m^2) were defined on the basis of WHO definitions. Similarly we considered WC as a categorical variable using three categories <94 cm, 94–101 cm and ≥102 cm. In multivariate analyses, smoking,social class, physical activity, alcohol intake, diabetes and stroke were fitted as categorical variables; leptin, adiponectin, NT-proBNP and muscle mass were fitted as continuous variables.

3. Results

During the mean follow-up period of 11 years there were 1340 deaths in all men. Fig. 1 shows the Kaplan-Meier survival estimates by BMI groups in the three groups of men. In men without CHD or HF, obesity and normal weight men showed similar survival rates with the lowest rates in overweight men (log rank test p = 0.0008). In both men with CHD without HF and in men with HF overweight and obesity were associated with higher survival rates than men with normal weight [log rank test p = 0.02 and p = 0.07 respectively].

3.1. BMI, body composition, adipokines and NT-proBNP

Table 1 shows the association between BMI and body composition, adipokines and NT-proBNP in the three groups. In all groups, normal weight (BMI 18.5–24.9 kg/m^2) was strongly associated with low muscle mass. In men without CHD or HF over half of the men with normal weight had low muscle mass compared to just 7% in the obese group. The prevalence of low muscle mass in normal weight groups increased to 66% in those with CHD and to over 70% in those with HF. Central