Total body fat and the risk of Barrett's oesophagus – A bioelectrical impedance study

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ABSTRACT

Background: Body mass index is associated with the risk of Barrett's oesophagus (BO). It is uncertain whether this is related to total body fat or other factors that correlate with body mass index. We aimed to quantify the association between total body fat (measured by bioelectrical impedance) and risk of BO and examine if this association was modified by gastro-oesophageal reflux (GOR) and abdominal obesity.
Methods: In 2007–2009, we surveyed 235 cases (69% Males, Mean age 62.1 years) and 244 age and sex matched population controls from a population based case–control study of BO. We conducted structured interviews, standard anthropometry and bioimpedance analysis of total body fat. Odds ratios (OR) and 95% confidence intervals (CI) were estimated using multivariable logistic regression analysis.
Results: There was a significantly increased risk of BO among those in the highest tertile of total body fat weight (OR 2.01; 95%CI 1.26–3.21) and total body fat percentage (OR 1.86; 95%CI 1.10–3.15). These risks were largely attenuated after adjustment for GOR and waist circumference. There was a significantly increased risk of BO among those in the highest tertile of waist circumference (OR 2.21; 95%CI 1.39–3.51) and this was minimally attenuated after adjustment for total body fat and moderately attenuated after adjustment for GOR.
Conclusions: Total body fat is associated with an increased risk of BO but this appears to be mediated via both abdominal obesity and GOR. These findings provide evidence that abdominal obesity is more important than total body fat in the development of BO.

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1. Introduction

Obesity is defined as the accumulation of excessive body fat that may impair health [1]. Body mass index (BMI) has long been used as a surrogate measure for total body fat, but recent studies have shown that BMI correlates only modestly with total body fat, particularly with increasing age, increasing muscle mass and at the extremes of BMI [2,3]. Direct measurement of total body fat has previously been difficult and expensive requiring whole body plesmography or dual-energy X-ray absorptiometry. Bioimpedance analysis (BIA) is a simple, cheap, highly reproducible bedside technique that accurately measures total body fat [4–6].

Obesity has been associated with a number of cancers, including oesophageal adenocarcinoma (OA) [7–9]. Barrett's oesophagus (BO) is a metaplastic change in the distal oesophagus and is the precursor of OA [10–12]. There is conflicting evidence as to whether obesity is associated with an increased risk of BO. A meta-analysis has shown the risk of BO increases monotonically with BMI (OR 1.02 per kg/m^2; 95%CI 1.01–1.04), most likely mediated through gastro-oesophageal reflux (GOR) [13]. Moderate heterogeneity was found in the included studies. A subsequent cohort study has shown that in females, a high BMI $\geq$30 kg/m^2 was associated with an increased risk of BO (OR 1.52; 95%CI 1.02–2.28)

and this risk persisted after adjustment for GOR symptoms [14]. In contrast, a recent study, predominantly in males, found no association between a high BMI and risk of BO but did find an association between abdominal obesity and risk of BO [15].

The heterogeneity of the previously reported studies may be related in part to the limitations of BMI in accurately reflecting total body fat among different populations. A recent clinic based case–control study of 70 predominately male BO cases has suggested that total body fat mass, measured by BIA, is not associated with an increased risk of BO [16]. Given the modifiable nature of obesity as a risk factor, an understanding of the association between obesity, abdominal obesity and BO is important in developing preventive strategies for both BO and OA.

In this study we sought to determine whether there is an association between total body fat measured by BIA and risk of BO, and if present, is this association modified by adjusting for GOR symptoms and abdominal obesity.

2. Methods

This study was nested within the Study of Digestive Health (SDH), a population-based case–control study of BO conducted between 2003 and 2006 and previously described [17]. Cases were people aged 18–79 years newly diagnosed with BO defined as the presence of intestinal metaplasia (columnar epithelium with goblet cells) in a biopsy taken from the oesophagus by upper gastrointestinal endoscopy, regardless of the extent of involved mucosa. Control participants from the same geographic region were randomly selected from the Australian Electoral Roll (enrolment is compulsory by law in Australia), frequency matched by sex and age (in 5-year age groups) to the case series. Approval to undertake the study was obtained from the Human Research Ethics Committee of the Queensland Institute of Medical Research in 2007. We obtained written informed consent from case patients and control participants. Those who did not speak English, were too ill to participate or moved out of the geographical study area were excluded.

2.1. Study participants

From 2007 to 2009, BO cases and population controls that took part in the SDH were contacted via a series of letters and telephone calls inviting them to take part in this anthropometric study. All 359 BO cases from the SDH were approached to take part in the current study. 235 (65%) of these patients completed the study, 69 (20%) declined to participate and 55 (15%) were found to be ineligible due to factors including being too ill, having moved from the study area, the presence of contraindications to BIA and death. 419 age and sex matched population controls were approached to take part in the current study. 244 (58%) of these controls completed the study, 108 (26%) declined to participate and 67 (16%) were found to be ineligible.

2.2. Data collection

Data were collected from participants through structured, self-completed questionnaires, followed by a standardized interview, anthropometric measurements and BIA conducted by a trained research nurse from 2007 to 2009. We collected information in the questionnaire and interview about current and previous GOR symptoms, current and past smoking, alcohol and recent use of other medications including aspirin and non-steroidal anti-inflammatory drugs (NSAID).

At interview, the following anthropometric measures were collected using standardized protocols (see Supplementary File: Appendix 1 online for details of protocol): Height, weight, body

mass index (BMI) and waist circumference. Body impedance was measured using a calibrated bioelectrical impedance analyzer (Bodystat 1500 (50 MHz) – Bodystat Ltd, Isle of Man) according to a standardized protocol with subjects instructed to fast for 4 hours before the analysis. Electrodes were placed on the ipsilateral hand and foot in the supine position. (see Appendix 1 online for protocol). Total body fat (weight and percentage) and fat free weight were calculated by the machine's software based on body impedance. Prior to the commencement of the study, we performed same-day, paired analyses on 23 healthy volunteers (18 females, 5 males, age range 23–61 years) to assess reproducibility. We observed coefficients of variation of 2% for total body fat weight and 1.9% for total body fat percentage.

2.3. Statistical analyses

The primary aim of the analysis was to measure the associations between measures of total body fat and risk of BO and then to assess whether the effects were modified by adjusting for GOR symptoms and abdominal obesity. We used the BIA measures of total body fat weight (TBFW) and total body fat weight as a percentage of total body weight (TBF%) for analysis. Mean and standard deviations where used to describe measures of central tendency for continuous variables. A t-test was used to test for differences between cases and controls for continuous measures. Chi-square tests were used to test for differences between cases and controls for categorical variables. To estimate the relative risk of BO associated with measures of total body fat, BMI, waist circumference, aspirin and NSAID use, alcohol intake and GOR symptoms, we calculated the odds ratio (OR) and 95% confidence interval (95%CI) by unconditional multivariable logistic regression analysis. For measures of total body fat, BMI and waist circumference we fitted models that contained terms for each measure as a categorical variable according to WHO categories for BMI (underweight and normal $-<25$ kg/m^2, overweight -25 to 29.9 kg/m^2 and obese ≥ 30.0 kg/m^2) [1] and sex-specific tertile cutpoints in the control distribution for the other measures, adjusting for exact age in years, sex and smoking status. BMI <25 kg/m^2 and the lowest tertile for each categorical variable were used as the reference category. For smoking and GOR symptoms, we fitted models that contained terms for each as a categorical variable (smoking: never smoked (reference category), ex-smoker and current smoker; gastro-oesophageal reflux: never gastro-oesophageal reflux symptoms (reference category), worst GOR symptoms weekly or less often, worst GOR symptoms more than weekly). We fitted further models for measures of total body fat and waist circumference that simultaneously adjusted for each other and also for GOR symptoms. To test for trend, categorical variables were included in the model as continuous data (with category values taking the median of the category) and the Wald test was used as an approximation of the Mantel extension chi-square with 1 degree of freedom. Correlation between measures of total body fat and BMI and waist circumference were measured using Pearson's correlation coefficient (r). We also performed stratified analyses for sex. Statistical significance was determined at $\alpha = .05$, and all tests for statistical significance were two-sided. Analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA).

To explore the shape of the dose–response relationship between measures of total body fat and risk of BO, we fitted an age and sex-adjusted logistic regression model with restricted cubic spline for TBFW and TBF% by means of generalized additive logistic models (CRAN package mgcv in R software). Smoothing splines fixed at 3 degrees of freedom, resulting in placements of knots equally through the data, were used to test for significance of nonlinearity against the linear effect.