Metabolic syndrome, Barrett’s oesophagus, the risk of oesophageal adenocarcinoma and statin treatment

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ABSTRACT: Barrett’s oesophagus (BO) is a proinflammatory condition principally induced by gastro-esophageal reflux disease. There is a strong association between metabolic syndrome (MetS) and its components, mainly increased waist-to-hip ratio, hypertension, and hypertriglyceridaemia, with increased risk for BO and oesophageal adenocarcinoma. At present there are generally accepted preventive interventions that reduce the incidence of obesity (MetS)-associated oesophageal cancer. However, observational studies suggest that the combined use of a statin and aspirin is associated with significantly reduced incidence of cancer in patients with BO. Moreover, there appears to be a significant association between the use of statins and a reduced incidence of all oesophageal cancers, including oesophageal adenocarcinoma, regardless of the presence of BO, obesity, or reflux disease. Thus, statins might have clinically important antineoplastic off-target effects that should be further explored in

Metabolikó sýndrómo, oiosofágos Barrett, kínidunou adevnikarkiniómatoj tou oiosofágou kai hé therapeía mé stastínes

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ΠΕΡΙΛΗΨΗ: Ο Οισοφάγος Barrett (BO) είναι μια φλεγμονώδης κατάσταση που προκαλείται κυρίως από γαστροοισοφαγική παλινδρόμηση. Υπάρχει μια σχετική συσχέτιση μεταξύ του μεταβολικού σύνδρομου (MS) και των συστατικών του, κυρίως του αυξημένου λόγου μέσης-ισχίου, της αρτηριακής υπέρτασης, και της υπερτριγλυκεριδαιμίας, με αυξημένο κίνδυνο για BO και του οιοσφάγου αδενοκαρκίνωμα. Προς το παρόν δεν υπάρχουν γενικά αποδεκτές προληπτικές παρεμβάσεις που μειώνουν τη συχνότητα εμφάνισης της καρκίνου του οισοφάγου που συνδέεται με την παχυσαρκία-MS. Ωστόσο, μελέτες παρατήρησης δείχνουν ότι η συνδυασμένη χρήση μιας στατινός και ασπιρίνης συνδέεται με σημαντικά μειωμένη συχνότητα εμφάνισης καρκίνου του οισοφάγου σε ασθενείς με BO. Επιπλέον, χρησιμοποιείται η συνδυασμένη χρήση μιας στατικής και ασπιρίνης να συνδέεται με σημαντικά μειωμένη συχνότητα εμφάνισης καρκίνου του οισοφάγου σε ασθενείς με BO.
Barrett’s oesophagus (BO) is an adaptation of the oesophagus to the proinflammatory state principally induced by gastroesophageal reflux disease (GERD). There appears to be a strong association between metabolic syndrome (MetS) and increased risk for BO. This association is mostly mediated by the role of central adiposity in the pathogenesis of BO, which is observed even in patients without GERD. Patients with MetS almost 60% higher risk for BO and this risk is proportional to the number of MetS components (p for trend <0.001); when all five MetS components are present, the odds ratio for BO is 2.61 (95% confidence interval (CI) 1.14–5.99). Among the MetS components, increased waist-to-hip ratio, hypertension and hypertriglyceridaemia were independently associated with increased risk of BO. However, MetS might confer additional risk of BO independently of obesity. This was shown in a meta-analysis of 40 observational studies that reported that central adiposity, independently of body mass index (BMI), was associated with oesophageal inflammation, metaplasia and neoplasia, and this relationship was mediated by both gastroesophageal reflux-dependent and -independent mechanisms. It appears that this association is not only due to the increased intra-abdominal pressure in patients with visceral adiposity, which predisposes to GERD and finally BO, but other mechanisms are also implicated. These might include altered intestinal microbiota, MetS-associated low-grade inflammation induced by obesity, and secretion of mediators by adipocytes, which may directly influence the oesophageal epithelium. Indeed, increased leptin levels have been independently associated with progression to oesophageal adenocarcinoma and in laboratory studies leptin enhances carcinogenesis in certain cell lines. Adiponectin is also secreted by adipocytes and its serum levels are reduced in obese patients; decreased adiponectin levels are associated with progression of BO to oesophageal adenocarcinoma and in vitro studies showed that adiponectin exerts antineoplastic effects in BO cell lines and inhibits growth factor signalling. Thus, it becomes clear that MetS is not just a risk factor for type 2 diabetes mellitus or cardiovascular disease (CVD), but might also increase the risk for BO and oesophageal adenocarcinoma, given that BO is a well-recognized precursor of oesophageal high-grade dysplasia and oesophageal adenocarcinoma. The Seattle Barrett’s Oesophagus Study showed that insulin resistance and increased levels of leptin are associated with increased risk for oesophageal adenocarcinoma, whereas increased levels of high-molecular-weight adiponectin is associated with reduced risk of oesophageal adenocarcinoma. Therefore, measurement of these adipokines might be used to determine cancer risk among patients with BO.

At present there are no established preventive interventions that reduce the incidence of obesity-associated oesophageal cancer. However, observational studies suggest that the combined use of a statin and aspirin is associated with significantly reduced incidence of cancer in patients with BO. A meta-analysis of studies in patients with BO showed that the use of statins (OR 0.57, 95% CI 0.43–0.75) and cyclo-oxygenase inhibitors (OR 0.59, 95% CI 0.45–0.77) were independently associated with a reduced incidence of oesophageal adenocarcinoma. Combined use of a statin plus cyclo-oxygenase inhibitor was associated with an even lower incidence of oesophageal adenocarcinoma (OR=0.26, 95% CI 0.10–0.68). Moreover, 6 studies evaluated the...
potential role of statin use in reducing the risk for all oesophageal cancers.\textsuperscript{14-19} One of the studies\textsuperscript{14} was a meta-analysis that included 371,203 oesophageal cancers and 608,3150 controls. A significant reduction in the risk for oesophageal cancers in both men and women was observed in subjects treated with simvastatin and atorvastatin, but not in those treated with pravastatin or rosuvastatin.\textsuperscript{14} Another study\textsuperscript{15} showed that after adjustment for covariates, patients receiving atorvastatin for more than 12 months had lower risk for oesophageal cancer compared with those not on a statin (OR 0.14, 95% CI 0.04–0.56).\textsuperscript{15} Other statins did not show an association with the incidence of oesophageal cancer.\textsuperscript{15}

Overall, these preliminary data suggest that MetS is related to an increased risk of BO and oesophageal adenocarcinoma. Moreover, there appears to be a significant association between the use of statins and a reduced incidence of all oesophageal cancers, including oesophageal adenocarcinoma, regardless of the presence of BO, obesity, or GERD.\textsuperscript{20,21} This suggests that statins might have clinically important antineoplastic off-target effects that should be further explored in interventional studies. It should also be tested whether different statins or different doses are similarly effective in reducing the risk for BO and oesophageal adenocarcinoma. Lifestyle measures to reduce the prevalence and incidence of MetS might be also useful in preventing these potentially fatal diseases and their role should also be evaluated in prospective studies.

**Declaration of interest**

There is no conflict of interest for all authors.

**References**


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