Hellenic Journal of Atherosclerosis 6(2):83–85

Ελληνική Επιθεώρηση Αθηροσκλήρωσης 6(2):83–85

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

Chr. Boutari,[1] St.M. Angelopoulou,[2] G. Sfikas,[1] K. Kaitanidis,[1] K. Tziomalos,[2] V.G. Athyros[1]

[1]2nd Propedeutic Department of Internal Medicine, Medical School, Aristotle University of Thessaloniki, "Hippocration" Hospital, Thessaloniki, [2]1st Propedeutic Department of Internal Medicine, Medical School, Aristotle University of Thessaloniki, "AHEPA" Hospital, Thessaloniki, Greece

Μεταβολικό σύνδρομο, οισοφάγος Barrett, κίνδυνος αδενοκαρκινώματος του οισοφάγου και η θεραπεία με στατίνες

Χρ. Μπουτάρη,[1] Στ.Μ. Αγγελοπούλου,[2] Γ. Σφήκας,[1] Κ. Καϊτανίδης,[1] Κ. Τζιόμαλος,[2] Β.Γ. Άθυρος[1]

[1]Β΄ Προπαιδευτική Παθολογική Κλινική, Ιατρική Σχολή, Αριστοτέλειο Πανεπιστήμιο Θεσσαλονίκης, «Ιπποκράτειο» Νοσοκομείο, Θεσσαλονίκη, [2]Α΄ Προπαιδευτική Παθολογική Κλινική, Ιατρική Σχολή, Αριστοτέλειο Πανεπιστήμιο Θεσσαλονίκης, Νοσοκομείο «ΑΧΕΠΑ», Θεσσαλονίκη

ABSTRACT: Barrett's oesophagus (BO) is a proinflammatory condition principally induced by gastroesophageal 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

ΠΕΡΙΛΗΨΗ: Ο Οισοφάγος Barrett (BO) είναι μια φλεγμονώδης κατάσταση που προκαλείται κυρίως από γαστροοισοφαγική παλινδρόμηση. Υπάρχει μια ισχυρή συσχέτιση μεταξύ του μεταβολικού συνδρόμου (ΜΣ) και των συστατικών του, κυρίως του αυξημένου λόγου μέσης-ισχίων, της αρτηριακής υπέρτασης, και της υπερτριγλυκεριδαιμίας, με αυξημένο κίνδυνο για ΒΟ και του οισοφάγου αδενοκαρκίνωμα. Προς το παρόν δεν υπάρχουν γενικά αποδεκτές προληπτικές παρεμβάσεις που μειώνουν τη συχνότητα εμφάνισης του καρκίνου του οισοφάγου που συνδέεται με την παχυσαρκία-ΜΣ. Ωστόσο, μελέτες παρατήρησης δείχνουν ότι η συνδυασμένη χρήση μιας στατίνης και ασπιρίνης συνδέεται με σημαντικά μειωμένη συχνότητα εμφάνισης καρκίνου του οισοφάγου σε ασθενείς με ΒΟ. Επιπλέον, φαίνεται να υπάρχει σημαντική συσχέτιση μεταξύ της χρήσης στατινών και μειωμένη συχνότητα εμφάνισης όλων των καρκίνων του οισοφάγου, συμπεριλαμβανομένου του αδενοκαρκινώματος, ανεξάρτητα από την

Vasilios G. Athyros, MD, FESC, FRSPH, FASA, FACS
15 Marmara street, GR-551 32 Thessaloniki, Greece
Tel: (+30) 2310-892 606, Fax: (+30) 2310-835 955
e-mail: vathyros@gmail.com – athyros@med.auth.gr

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Βασίλειος Γ. Άθυρος, MD, FESC, FRSPH, FASA, FACS
Μαρμαρά 15, 551 32 Θεσσαλονίκη
Τηλ: 2310-892 606, Fax: 2310-835 955
e-mail: vathyros@gmail.com – athyros@med.auth.gr

interventional studies. All the above suggest that it should be tested whether different statins or different doses are similarly effective in reducing the risk for BO and oesophageal adenocarcinoma.

Key words: Metabolic syndrome, Barrett's oesophagus, oesophageal adenocarcinoma, statins.

παρουσία του ΒΟ, παχυσαρκίας, ή γαστροοισοφαγικής παλινδρόμησης. Έτσι, οι στατίνες μπορεί να έχουν κλινικά σημαντικές αντινεοπλασματικές δράσεις (εκτός της κύριας θεραπευτικής τους δράσης) που θα πρέπει να διερευνηθεί περαιτέρω σε επεμβατικές μελέτες. Όλα τα παραπάνω δείχνουν ότι πρέπει να δοκιμαστεί αν διάφορες στατίνες ή διαφορετικές δόσεις τους είναι ομοίως αποτελεσματικές στη μείωση του κινδύνου για ΒΟ και το οισοφαγικό αδενοκαρκίνωμα.

Λέξεις ευρετηρίου: Μεταβολικό σύνδρομο, οισοφάγος Barrett, αδενοκαρκίνωμα του οισοφάγου, στατίνες.

Barrett's oesophagus (BO) is an adaptation of the oesophagus to the proinflammatory state principally induced by gastroesophageal reflux disease (GERD).[1] There appears to be a strong association between metabolic syndrome (MetS) and increased risk for BO.[1] This association is mostly mediated by the role of central adiposity in the pathogenesis of BO, which is observed even in patients without GERD.[1,2] 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).[2] Among the MetS components, increased waist-to-hip ratio, hypertension and hypertriglyceridaemia were independently associated with increased risk of BO.[2] However, MetS might confer additional risk of BO independently of obesity.[2] 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.[3] 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.[3,4] 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.[4] Indeed, increased leptin levels have been independently associated with progression to oesophageal adenocarcinoma and in laboratory studies leptin enhances carcinogenesis in certain cell lines.[4] 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 anticancer effects in BO cell lines and inhibits growth factor signalling.[4] 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.[5] 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.[6] Therefore, measurement of these adipokines might be used to determine cancer risk among patients with BO.[6]

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.[7,8] A meta-analysis of studies[9–13] 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.[8] 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).[8] Moreover, 6 studies evaluated the

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potential role of statin use in reducing the risk for all oesophageal cancers.[14–19] One of the studies[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 man and women was observed in subjects treated with simvastatin and atorvastatin, but not in those treated with pravastatin or rosuvastatin.[14] Another study[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).[15] Other statins did not show an association with the incidence of oesophageal cancer.[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.[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

1. Drahos J, Ricker W, Parsons R et al. Metabolic syndrome increases risk of Barrett esophagus in the absence of gastroesophageal reflux: an analysis of SEER-Medicare Data. *J Clin Gastroenterol* 2015, 49:282–288
2. Thrift AP, Hilal J, El-Serag HB. Metabolic syndrome and the risk of Barrett's oesophagus in white males. *Aliment Pharmacol Ther* 2015, 41:1182–1189
3. Singh S, Sharma AN, Murad MH et al. Central adiposity is associated with increased risk of esophageal inflammation, metaplasia, and adenocarcinoma: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2013, 11:1399–1412.e7.
4. Long E, Beales IL. The role of obesity in oesophageal cancer development. *Therap Adv Gastroenterol* 2014, 7:247–268
5. Yousef F, Cardwell C, Cantwell MM et al. The incidence of esophageal cancer and high-grade dysplasia in Barrett's esophagus: a systematic review and meta-analysis. *Am J Epidemiol* 2008, 168:237–249
6. Duggan C, Onstad L, Hardikar S et al. Association between markers of obesity and progression from Barrett's esophagus to esophageal adenocarcinoma. *Clin Gastroenterol Hepatol* 2013, 11:934–943
7. Ogunwobi O, Beales I. Statins inhibit proliferation and induce apoptosis in Barrett's esophageal adenocarcinoma cells. *Am J Gastroenterol* 2008, 103:825–837
8. Beales I, Hensley A, Loke Y. Reduced esophageal cancer incidence in statin users, particularly with cyclo-oxygenase inhibition. *World J Gastrointest Pharmacol Ther* 2013, 4:69–79
9. Nguyen DM, El-Serag HB, Henderson L et al. Medication usage and the risk of neoplasia in patients with Barrett's esophagus. *Clin Gastroenterol Hepatol* 2009, 7:1299–1304
10. Kantor ED, Onstad L, Blount PL et al. Use of statin medications and risk of esophageal adenocarcinoma in persons with Barrett's esophagus. *Cancer Epidemiol Biomarkers Prev* 2012, 21:456–461
11. Nguyen DM, Richardson P, El-Serag HB. Medications (NSAIDs, statins, proton pump inhibitors) and the risk of esophageal adenocarcinoma in patients with Barrett's esophagus. *Gastroenterology* 2010, 138:2260–2266
12. Kastelein F, Spaander MC, Biermann K et al. Nonsteroidal anti-inflammatory drugs and statins have chemopreventative effects in patients with Barrett's esophagus. *Gastroenterology* 2011, 141:2000–2008
13. Beales IL, Vardi I, Dearman L. Regular statin and aspirin use in patients with Barrett's oesophagus is associated with a reduced incidence of oesophageal adenocarcinoma. *Eur J Gastroenterol Hepatol* 2012, 24: 917-923
14. Hippisley-Cox J, Coupland C. Unintended effects of statins in men and women in England and Wales: population based cohort study using the QResearch database. *BMJ* 2010, 340:c2197
15. Lai SW, Liao KF, Lai HC et al. Atorvastatin correlates with decreased risk of esophageal cancer: a population-based case-control study from Taiwan. *Libyan J Med* 2012, 7:18830
16. Vinogradova Y, Coupland C, Hippisley-Cox J. Exposure to statins and risk of common cancers: a series of nested case control studies. *BMC Cancer* 2011, 11:409
17. Kaye JA, Jick H. Statin use and cancer risk in the General Practice Research Database. *Br J Cancer* 2004, 90: 635–637
18. Friedman GD, Flick ED, Udaltsova N et al. Screening statins for possible carcinogenic risk: up to 9 years of follow-up of 361,859 recipients. *Pharmacoepidemiol Drug Saf* 2008, 17:27–36
19. Bhutta HY, Clark A, Holt S et al. Oesophageal cancer - an aetiological investigation into the potential protective effect of statins in the UK general practice research database (GPRD). *Gut* 2011, 60: A36–A37
20. Bhutta HY, Alexandre L, Clark A. Do statins prevent the histological subtypes of oesophageal cancer? Prospective data from the UK General Practice Database (GPRD). *Gut* 2012, 61: A299–A300
21. Beales IL, Vardi I, Dearman L et al. Statin use is associated with a reduction in the incidence of esophageal adenocarcinoma: a case control study. *Dis Esophagus* 2013, 26:838–846

Ημερομηνία Υποβολής 10/05/2015
Ημερομηνία Αποδοχής 26/05/2015

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