Association between body mass index and erosive esophagitis: A meta-analysis

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AIM: To conduct a meta-analysis to estimate the determinants of the association between erosive esophagitis (EE) and body mass index (BMI).

METHODS: We identified the studies using PubMed. Studies were selected for analysis based on certain inclusion and exclusion criteria. Data were extracted from each study on the basis of predefined items. Meta-analyses were performed to verify the risk factors, such as obesity and gender.

RESULTS: Twenty-one studies were included in this systematic review. These studies demonstrated an association between increasing BMI and the presence of EE (95% confidence interval (CI): 1.35-1.88, overweight, odds ratio (OR) = 1.60, P value homogeneity = 0.003, 95% CI: 1.65-2.55, obese, OR = 2.05, P < 0.01]. The heterogeneity disappeared by stratifying for gender. No publication bias was observed in this meta-analysis by the Egger method.

CONCLUSION: This analysis demonstrates a positive association between BMI and the presence of EE, especially in males. The risk seems to progressively increase with increasing weight.

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Key words: Erosive esophagitis; Gastroesophageal reflux disease; Obesity; Body mass index; Meta-analysis

INTRODUCTION

The symptoms of gastroesophageal reflux disease (GERD) are common health problems in industrialized societies. It is a highly prevalent gastrointestinal disorder encountered in clinical practice[1,2]. Erosive esophagitis (EE) is one of the most common forms of GERD. It occurs when excessive reflux of acid and pepsin results in necrosis of surface layers of the esophageal mucosa, thus causing erosions and...
MATERIALS AND METHODS

Search strategy

Two investigators independently performed a systematic search of all existing English-language literatures published up to April 2011 using PubMed, an electronic search engine for published manuscripts. Search terms included “obesity”, “BMI”, “overweight” or “BMI”, combined with “reflux” or “EE”. A total of 268 articles were identified after the preliminary search was reviewed in further details.

Study selection

Studies were included if they met all the following inclusion criteria: (1) Cross-sectional, case control, or cohort studies that permitted assessment of a causal relationship between BMI and EE; (2) Studies with documented and clearly-defined BMI in kg/m\(^2\) for all participants; (3) Studies that reported a relative risk or odds ratio (OR) with confidence intervals or provided sufficient data to permit their calculation; and (4) Studies with EE diagnosed by upper endoscopy. The inclusion criteria were not otherwise restricted by study size or publication type. The followings were chosen as the exclusion criteria: (1) Studies not limited to humans or not written in English; (2) Studies that did not report risk estimates or raw data to allow independent calculation of these estimates; and (3) Case reports, case series or studies that lacked a control group.

Data abstraction

The abstracted data included information on the source of the study population, study design (case control, cohort, or cross-sectional), length of the study period, primary aim of the study, study definitions (BMI definitions of normal, overweight or obese), exposure measurement method (self-reported vs measured BMI), outcome definitions (diagnosis of EE with endoscopy), total number of subjects with EE, case and control criteria, ORs or risk ratios with and without adjustment for potential confounders and potential confounders used for adjustment.

Outcome definition

An outcome was defined as EE diagnosed with endoscopy. The severity of EE was graded from A to D according to the LA classification\(^4\) or modified Savary-Miller classification (grade I, single or multiple non-confluent erosions; grade II, confluent non-circumferential multiple erosion; grade III, circumferential erosions; and grade IV, ulcer and/or stricture)\(^23\).

Statistical analysis

The BMI data were extracted from each study and analyzed with STATA 11.0 (StataCorp, College Station, TX, United States, www.stata.com). Summary OR estimates were calculated using either relative risks (for cohort stud-
We identified 268 published articles or abstracts (Figure 1). After review of titles and abstracts, 31 articles appeared to meet the initial inclusion criteria. The excluded studies were review articles, animal experiments, case series that lacked appropriate control groups and studies that did not report the subject of interest. These 31 studies underwent a complete data abstraction. Ten additional studies were excluded after data abstraction for the following reasons: BMI categories that were inconsistent with the proposed reference ranges[37,39-41], inconsistent outcome definition[37], lack of proper control group[38], and lack of evaluable risk estimates within the proposed categories[39-41].

The remaining 21 studies[8,12,42-59] (i.e., four cross-sectional, three cohort, 14 case control studies) were included in the primary analysis (Tables 1 and 2). Twelve studies were conducted for the primary purpose of evaluating the relationship between BMI and EE[8,44,45,49-52,54,55,57-59], eight studies were conducted to identify the variety of risk factors for EE, including BMI[8,12,42,46-48,53,56], and one study described the clinical characteristics of EE and non-erosive reflux disease, including BMI[43]. In Table 1, controls and normal groups were composed of general population and healthy volunteers. Eighteen studies were included in Table 3 because of their stratification by gender.

The pooled OR of EE related to BMI of 25 kg/m² or higher was 1.64-fold greater than that of EE related to BMI less than 25 kg/m² (OR, 1.64, 95% CI: 1.45-1.85, test for homogeneity, P = 0.000, I² = 65.7%) (Figure 2, Table 3). Stratification by gender and BMI category showed a homogeneous positive association between increased BMI and EE, and the strength of the association with increased BMI and EE, and the strength of the association with increased BMI (Table 3). The risk for overweight males (OR, 1.40, 95% CI: 1.11-1.75, P = 0.285) increased further for obese males (OR, 1.75, 95% CI: 1.02-2.96, P = 0.099) (Figure 3). The pooled OR in females and males for BMI greater than 25 kg/m² were 1.45 (95% CI: 1.26-1.66) and 1.52 (95% CI: 1.24-1.87), respectively. Therefore, we considered there was a strong positive association between increasing BMI and EE in males, but not in females.

**Evaluation of heterogeneity**

The initial summary estimates for EE were heterogeneous, as described above. Stratification by BMI category did not substantially resolve the heterogeneity; however, additional stratification by gender provided more homogeneity. Stratification of the entire population by exposure measurement (e.g., self-report vs measured), or study design (case control vs cohort) did not substantially influence the initial heterogeneity (Table 3).

**Publication bias**

The rank correlation test did not suggest the presence of publication bias for the main summary estimates for either the overweight (P = 0.656) or the obese and overweight (P = 0.804). A review of funnel plots did not demonstrate patterns strongly suggestive of publication bias (Figure 4).

**DISCUSSION**

Our pooled results of observational studies demonstrated a positive association between increased BMI and the risk of EE. The strength of the association increased with increasing BMI and there was a trend towards a stronger association in males than in females. Unlike other non-modifiable risk factors such as age, race and gender, BMI is potentially modifiable. Thus, identifying a relationship...
between obesity and EE might have significant implications for counseling.

A recent meta-analysis of BMI and GERD complications found heterogeneous results and it was not able to identify strata with homogeneous results. It was possibly due to their methods of stratification, the utilization of estimates with markedly different measures of BMI association, the absence of studies included in the current analysis, and the inclusion of studies that did not set up a non-GERD control group. In contrast, in the cur-

### Table 1: Study characteristics

| Authors | Yr | Design  | Region    | Population size | Case population | Reference population | Confounders adjusted for |
|---------|----|---------|-----------|-----------------|------------------|-----------------------|--------------------------|
| Ha et al[43] | 2010 | Case-control | South Korea | n = 292 (EE), n = 500 (NERD) | Single hospital | Hospital controls | G, E, T, J, OD, WHR, TG |
| Nam et al[60] | 2010 | Cohort | South Korea | n = 495 (EE), n = 3779 (normal) | General population | General population | WC, WHR, VAT, SAT |
| Wang et al[48] | 2010 | Case-control | China | n = 70 (EE), n = 502 (non-EE) | General population | General population | A, G, S, B, T, E, C, tea drinking, spicy food consumption, betel nut use |
| Koo et al[54] | 2009 | Case-control | South Korea | n = 42 (EE), n = 987 (control) | General population | General population | G, T, E, TG |
| Chua et al[57] | 2009 | Case-control | Taiwan, China | n = 427 (EE), n = 639 (EE) | Single hospital | Hospital controls | TG, Glucose intolerance, HDL-C, SBP |
| Song et al[56] | 2009 | Case-control | South Korea | n = 5443 (non-EE) | Single hospital | Hospital controls | A, G, T, E, H, TC, HL-D, LDL-C, TG, BP, fasting glucose |
| Lien et al[45] | 2009 | Case-control | Taiwan, China | n = 102 (EE), n = 1492 (non-EE) | Single hospital | Hospital controls | A, E, T |
| Chung et al[52] | 2008 | Case-control | South Korea | n = 3539 (EE), n = 3539 (control) | Single hospital | Hospital controls | E, T, metabolic syndrome |
| Moki et al[57] | 2007 | Cross-sectional | Japan | n = 191 (EE), n = 4968 (non-EE) | General population | General population | A, G, T, B, hypertension, lifestyle choices, abdominal obesity, concomitant medications, concomitant medications, concomitant medications |
| Kang et al[48] | 2007 | Case-control | South Korea | n = 26229 (non-EE), n = 1810 (EE) | Single hospital | Hospital controls | A, G, J |
| Labenz et al[59] | 2004 | Cross-sectional | Germany | n = 2435 (EE), n = 2834 (control) | Medical center | Medical center | A, G, T, B, hypertension, lifestyle choices, abdominal obesity, concomitant medications, concomitant medications, concomitant medications |
| Nilsson et al[50] | 2002 | Case-control | Sweden | n = 179 (EE), n = 1024 (control) | Multiple hospital | Multiple hospital | T, cholecystectomy, I, drugs use |
| Wilson et al[54] | 1999 | Case-control | United States | n = 179 (control) | Single hospital | Single hospital | A, G, J, R |
| Steen-Larsen et al[52] | 1988 | Cross-sectional | Sweden | n = 195 (EE), n = 1029 (control) | Single hospital | Single hospital | None |

A: Age; B: Aspirin or NSAID intake; C: Coffee; D: Meal size; E: Alcohol/ethanol; F: Family history; G: Gender; H: *Helicobacter pylori* infection; I: Asthma or asthma medication; J: Hiatal hernia; K: Hospital visit or hospitalization; M: Marital status; O: Symptom checklist-90 score; P: Physical activity; Q: Psychosomatic symptoms; R: Race; S: Socioeconomic status, education; T: Tobacco; W: Right handedness; V: Comorbidity; X: Case control status; Y: Birthplace; Z: Hormone replacement therapy; VAT: Visceral adipose tissue; SAT: Subcutaneous adipose tissue; BP: Blood pressure; SBP: Systolic; DBP: Diastolic blood pressure; TC: Total cholesterol; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; TG: Triglyceride; HBAlc: Hemoglobin A1c; OD: Obesity degree; WHR: Waist-to-hip ratio; WC: Waist circumference; PBF: Percentage of body fat; FBG: Fasting blood glucose; EE: Erosive esophagitis; NERD: Non-erosive reflux disease; NSAID: Nonsteroidal antiinflammatory drugs.
### Table 2  Exposure and outcome definitions

| Authors                | Year | Exposure (source) | BMI reference (kg/m²) | Exposure (definitions) | Outcome (source) | Outcome (definitions) |
|------------------------|------|-------------------|-----------------------|------------------------|-----------------|-----------------------|
| Ha et al[50]           | 2010 | Measured BMI      | ≤ 25                  | BMI overweight (kg/m²) | BMI overweight   | Endoscopy  Los Angeles classification |
| Nam et al[51]          | 2010 | Measured BMI      | < 20                  | BMI overweight (kg/m²) | BMI overweight   | Endoscopy  Los Angeles classification |
| Wang et al[52]         | 2010 | Measured BMI      | < 25                  | BMI overweight (kg/m²) | BMI overweight   | Endoscopy  Los Angeles classification |
| Koo et al[53]          | 2009 | Measured BMI      | < 23                  | BMI overweight (kg/m²) | BMI overweight   | Endoscopy  Los Angeles classification |
| Koo et al[53]          | 2009 | Measured BMI      | < 23                  | BMI overweight (kg/m²) | BMI overweight   | Endoscopy  Los Angeles classification |
| Chua et al[54]         | 2009 | Self-report       | < 25                  | BMI overweight (kg/m²) | BMI overweight   | Endoscopy  Los Angeles classification |
| Song et al[55]         | 2009 | Measured BMI      | ≥ 25                  | BMI overweight (kg/m²) | BMI overweight   | Endoscopy  Los Angeles classification |
| Lien et al[56]         | 2009 | Self-report       | < 24                  | BMI overweight (kg/m²) | BMI overweight   | Endoscopy  Los Angeles classification |
| Lien et al[56]         | 2009 | Self-report       | < 24                  | BMI overweight (kg/m²) | BMI overweight   | Endoscopy  Los Angeles classification |
| Nam et al[57]          | 2009 | Self-report       | < 20                  | BMI overweight (kg/m²) | BMI overweight   | Endoscopy  Los Angeles classification |
| Lee et al[58]          | 2009 | Measured BMI      | 20-25                 | BMI overweight (kg/m²) | BMI overweight   | Endoscopy  Los Angeles classification |
| Chung et al[59]        | 2008 | Measured BMI      | < 23                  | BMI overweight (kg/m²) | BMI overweight   | Endoscopy  Los Angeles classification |
| Zagari et al[60]       | 2008 | Self-report       | 20-24.9               | BMI overweight (kg/m²) | BMI overweight   | Endoscopy  Los Angeles classification |
| Lee et al[61]          | 2008 | Measured BMI      | < 20                  | BMI overweight (kg/m²) | BMI overweight   | Endoscopy  Los Angeles classification |
| Kim et al[62]          | 2008 | Measured BMI      | < 23                  | BMI overweight (kg/m²) | BMI overweight   | Endoscopy  Los Angeles classification |
| Moki et al[63]         | 2007 | Measured BMI      | < 25                  | BMI overweight (kg/m²) | BMI overweight   | Endoscopy  Los Angeles classification |
| Kim et al[62]          | 2007 | Measured BMI      | 18.9-24.5             | BMI overweight (kg/m²) | BMI overweight   | Endoscopy  Los Angeles classification |
| Nocom et al[64]        | 2007 | Measured BMI      | 25-30                 | BMI overweight (kg/m²) | BMI overweight   | Endoscopy  Los Angeles classification |
| Kang et al[65]         | 2006 | Measured BMI      | < 25                  | BMI overweight (kg/m²) | BMI overweight   | Endoscopy  Los Angeles classification |
| Labenzi et al[66]      | 2004 | Measured BMI      | 25-30                 | BMI overweight (kg/m²) | BMI overweight   | Endoscopy  Los Angeles classification |
| Nilsson et al[67]      | 2002 | Self-report       | < 25                  | BMI overweight (kg/m²) | BMI overweight   | Endoscopy  Los Angeles classification |
| Wilson et al[68]       | 1999 | Measured BMI      | < 20                  | BMI overweight (kg/m²) | BMI overweight   | Endoscopy  NA |
| Steene-Larsen et al[69] | 1998 | Measured BMI      | < 25                  | BMI overweight (kg/m²) | BMI overweight   | Endoscopy  NA |

BMI: Body mass index; NA: Not available.

### Figure 2  Erosive esophagitis and body mass index (overweight and obese) in males and females.

The size of the square represents the weight that the corresponding study exerts in the meta-analysis. RR: Relative risk; OR: Odds ratio.

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\begin{table}
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\textbf{Authors}          & \textbf{Year} & \textbf{Exposure (source)} & \textbf{BMI reference (kg/m²)} & \textbf{Exposure (definitions)} & \textbf{Outcome (source)} & \textbf{Outcome (definitions)} \\
\hline
Ha et al[50]              & 2010         & Measured BMI              & ≤ 25                         & BMI overweight (kg/m²)        & BMI overweight           & Endoscopy  Los Angeles classification \\
Nam et al[51]             & 2010         & Measured BMI              & < 20                         & BMI overweight (kg/m²)        & BMI overweight           & Endoscopy  Los Angeles classification \\
Wang et al[52]            & 2010         & Measured BMI              & < 25                         & BMI overweight (kg/m²)        & BMI overweight           & Endoscopy  Los Angeles classification \\
Koo et al[53]             & 2009         & Measured BMI              & < 23                         & BMI overweight (kg/m²)        & BMI overweight           & Endoscopy  Los Angeles classification \\
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Chua et al[54]            & 2009         & Self-report               & < 25                         & BMI overweight (kg/m²)        & BMI overweight           & Endoscopy  Los Angeles classification \\
Song et al[55]            & 2009         & Measured BMI              & ≥ 25                         & BMI overweight (kg/m²)        & BMI overweight           & Endoscopy  Los Angeles classification \\
Lien et al[56]            & 2009         & Self-report               & < 24                         & BMI overweight (kg/m²)        & BMI overweight           & Endoscopy  Los Angeles classification \\
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Nam et al[57]             & 2009         & Self-report               & < 20                         & BMI overweight (kg/m²)        & BMI overweight           & Endoscopy  Los Angeles classification \\
Lee et al[58]             & 2009         & Measured BMI              & 20-25                        & BMI overweight (kg/m²)        & BMI overweight           & Endoscopy  Los Angeles classification \\
Chung et al[59]           & 2008         & Measured BMI              & < 23                         & BMI overweight (kg/m²)        & BMI overweight           & Endoscopy  Los Angeles classification \\
Zagari et al[60]          & 2008         & Self-report               & 20-24.9                      & BMI overweight (kg/m²)        & BMI overweight           & Endoscopy  Los Angeles classification \\
Lee et al[61]             & 2008         & Measured BMI              & < 20                         & BMI overweight (kg/m²)        & BMI overweight           & Endoscopy  Los Angeles classification \\
Kim et al[62]             & 2008         & Measured BMI              & < 23                         & BMI overweight (kg/m²)        & BMI overweight           & Endoscopy  Los Angeles classification \\
Moki et al[63]            & 2007         & Measured BMI              & < 25                         & BMI overweight (kg/m²)        & BMI overweight           & Endoscopy  Los Angeles classification \\
Kim et al[62]             & 2007         & Measured BMI              & 18.9-24.5                    & BMI overweight (kg/m²)        & BMI overweight           & Endoscopy  Los Angeles classification \\
Nocom et al[64]           & 2007         & Measured BMI              & 25-30                        & BMI overweight (kg/m²)        & BMI overweight           & Endoscopy  Los Angeles classification \\
Kang et al[65]            & 2006         & Measured BMI              & < 25                         & BMI overweight (kg/m²)        & BMI overweight           & Endoscopy  Los Angeles classification \\
Labenzi et al[66]        & 2004         & Measured BMI              & 25-30                        & BMI overweight (kg/m²)        & BMI overweight           & Endoscopy  Los Angeles classification \\
Nilsson et al[67]         & 2002         & Self-report               & < 25                         & BMI overweight (kg/m²)        & BMI overweight           & Endoscopy  Los Angeles classification \\
Wilson et al[68]          & 1999         & Measured BMI              & < 20                         & BMI overweight (kg/m²)        & BMI overweight           & Endoscopy  NA \\
Stene-Larsen et al[69]    & 1998         & Measured BMI              & < 25                         & BMI overweight (kg/m²)        & BMI overweight           & Endoscopy  NA \\
\hline
\end{tabular}
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BMI: Body mass index; NA: Not available.

### Figure 2  Erosive esophagitis and body mass index (overweight and obese) in males and females.

The size of the square represents the weight that the corresponding study exerts in the meta-analysis. RR: Relative risk; OR: Odds ratio.
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Table 3. Meta-analysis results in association between body mass index and erosive esophagitis

| BMI category | OR (95% CI) | P_homo (95%) | I² (%) | No. of studies |
|--------------|-------------|--------------|--------|----------------|
| Overall      |             |              |        |                |
| Overweight   | 1.60        | 0.003        | 59.8   | 15 [4,8,12,44-46,50,53,54,56-59] |
| Obese        | 2.05        | 0.000        | 74.2   | 15 [4,8,12,44-46,50,53,54,56-59] |
| Overweight + obese | 1.64       | 0.000     | 65.7   | 18 [4,8,12,45-47,50,53,54,56-59] |
| Females      |             |              |        |                |
| Overweight   | 1.47        | 0.011        | 7.4    | 3 [12,44,56]   |
| Obese        | 3.76        | 0.340        | 78.0   | 3 [12,44,56]   |
| Overweight + obese | 1.45      | 0.579      | 0.0    | 4 [12,44,55,56] |
| Males        |             |              |        |                |
| Overweight   | 1.40        | 0.285        | 20.8   | 4 [12,44,46,56] |
| Obese        | 1.74        | 0.099        | 52.1   | 4 [12,44,46,56] |
| Overweight + obese | 1.52       | 0.179     | 36.3   | 5 [12,44,46,55,56] |

BMI: Body mass index; OR: Odds ratio.

Figure 3. Erosive esophagitis and body mass index (overweight and obese) in males. The size of the square represents the weight that the corresponding study exerts in the meta-analysis. RR: Relative risk; OR: Odds ratio.

Figure 4. Evaluation of publication bias using a funnel plot. No significant funnel asymmetry was observed which could indicate publication bias. The horizontal line in the funnel plot indicates the random effects summary estimate, while the sloping lines indicate the expected 95% CI for a given standard error, assuming no heterogeneity between studies. Each trial is represented by a circle, the area of which represents the trial’s precision. Larger circles represent trials that offer more information.

Several hypotheses have been proposed to explain how obesity can cause EE. Abdominal fat may cause reflux through an increase in intrabdominal pressure and subsequent esophageal acid exposure. There was a suggestion that hormonal factors related to adiposity are more important than mechanical factors. Obesity is also associated with increased transient lower esophageal sphincter relaxation. Strengths of this analysis include the use of strict criteria for defining our outcome of interest and the consistency of the BMI-EE association within the males despite different patient populations and different study designs. All the included studies used endoscopy to confirm the diagnosis of EE, which eliminated the possibility of false positive EE cases. Also, we included stratification by study design, location, and source population.

There are potential limitations of this analysis. First, only observational studies were included; study results may be influenced by the presence of measured or unmeasured confounding factors, such as physical activity. Second, bias may also exist in the present study because unpublished data were not included, nor were conference abstracts or articles published in a language other than...
English. Third, the exposure definitions (i.e., normal, obese or overweight) differed slightly among the studies. We addressed this, however, by creating more comparable and consistent categories, although few differences still remained. Also, the accuracy of the BMI measurement and its reliability as a measure of adiposity are known to be imperfect.

In summary, based on our extensive review and synthesis of the literature, there appears to be a statistically significant association between elevated BMI and EE. Considering the prevalence of obesity and increasing incidence rates of EE, it is important to pay more attention to further studies that evaluate the influence of gender, ethnicity or age on EE to examine this association. Several studies have found visceral abdominal obesity to be an independent risk factor for EE[44,57]. Nam et al[44] demonstrated that association between EE and abdominal visceral adipose tissue volume was consistent among males and females, unlike the association between EE and BMI. However, CT or MRI is needed to test abdominal visceral adipose, which are time consuming and costly. So, measuring BMI may be more feasible. It is also important to determine whether weight loss can decrease the incidence of EE. Further studies are needed to evaluate the relationship between obesity and EE.

COMMENTS

Background

Both obesity and erosive esophagitis (EE) have a high prevalence worldwide. The relationship between them remains controversial.

Research frontiers

Many studies have been performed to evaluate the body mass index (BMI) for gastroesophageal reflux disease risk. It has been found that there was a positive correlation between BMI and EE in females, but not in males.

Innovations and breakthroughs

Findings from this meta-analysis suggested the importance of BMI in EE, especially in males.

Applications

This study provided the potential measurement indicators to identify high-risk groups for EE in obesity population, especially in males.

Terminology

BMI: BMI is a heuristic proxy for human body fat based on an individual’s weight and height. It is defined as the individual’s body mass divided by the square of his or her height. EE: EE is a term used to indicate any inflammation, swelling, or irritation of the esophagus. The esophagus becomes inflamed (swollen, irritated and red).

Peer review

The meta-analysis presents the data on association between obesity and EE. The topic is interesting and the methodology of the meta-analysis is appropriate.

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