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Correlation between serum homocysteine level and ulcerative colitis: A meta-analysis

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Abstract: Background: The aim of the present meta-analysis was to investigate the correlation of serum homocysteine (Hcy) concentration and ulcerative colitis (UC) through pooling all the relevant publications.

Methods The electronic databases of PubMed, EMBase, Web of Science, Google Scholar, CBM, and CNKI were systematic searched with the text words of homocysteine/Hcy, ulcerative colitis/UC, and inflammatory bowel disease. The correlation between serum Hcy and UC were demonstrated by stand mean difference (SMD) and corresponding 95% confidence interval (95% CI). The publication bias was evaluated by Egger's line regression test and Begg's funnel plot.

Results After systematic searching the related electronic databases of PubMed, EMBase, Web of Science, Google Scholar, CBM, and CNKI, eighteen publications relevant to serum Hcy and UC were included in the present meta-analysis. The serum Hcy levels were 14.01 ± 2.76 and 10.31 ± 1.59 $\mu\text{mol/L}$ for UC groups and healthy controls respectively with statistical difference ($p < 0.05$). Significant heterogeneity was found ($I^2 = 94.5\%$, $p < 0.001$) among the included studies. Therefore, the SMD was pooled through the random effect model. The pooled SMD was 1.20 (95% CI: 0.89–1.51), indicating that serum Hcy levels were significant higher in UC groups compared to healthy controls with statistical difference ($Z = 7.52$, $P < 0.001$). Egger's line regression test indicated no publications bias ($t = 1.45$, $p = 0.17$).

Conclusion: Serum Hcy levels were usually elevated in UC patients, which indicates that Hcy may play an

important role in UC development and may be used as a serological biomarker for UC diagnosis.

Keywords: Homocysteine; ulcerative colitis; meta-analysis; diagnosis.

Introduction

Homocysteine (Hcy), a sulfur-containing amino acid, is a product of methionine. Generally, homocysteine maintains a low level in serum in the human body under normal physiological conditions. Abnormally high levels of homocysteine in the serum, above $15 \mu\text{mol/L}$, is a medical condition called hyperhomocysteinemia [1]. Hyperhomocysteinemia was considered to be a significant risk factor for the development of a wide range of diseases, including thrombosis [2, 3], neuropsychiatric illness [4, 5], and fractures [6, 7]. Hyperhomocysteinemia is also found to be associated with microalbuminuria, which is a strong indicator of the risk of developing renal dysfunction [8, 9]. Recently, several studies have reported the elevated serum Hcy in UC patients compared to healthy controls [10, 11]. A meta-analysis has also evaluated the genetic variants of homocysteine/folate metabolism pathway and risk of inflammatory bowel disease [12]. However, meta-analysis relevant to serum Hcy concentration and ulcerative colitis was not discussed in the previous literature.

Material And Methods

Publications searching in the electronic databases

The electronic databases of PubMed, Embase, Web of Science, Google Scholar, CBM, and CNKI were systematic searched with the text words of homocysteine/Hcy, ulcerative colitis/UC, and inflammatory bowel disease. The publication inclusion criteria were (i) the publication type was a case-control or cohort study, (ii) the published

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language was English or Chinese, (iii) UC was confirmed in the case group, and (iv) serum Hcy levels in UC patients and healthy controls can be extracted from the original studies. The publication exclusion criteria were (i) other study types such as case report or review, (ii) inflammatory bowel disease other than UC, and (iii) duplicated published data or studies.

Publication review and data extraction from each of the included study

The full text of the studies included in the meta-analysis were reviewed by two reviewers (Yifang Zhong & Feng Yan) independently. The general information and important data were extracted from each of the original publication. The information included (i) the first and corresponding authors of the included studies, (ii) the sample size, (iii) the country of study performed, (iv) the age of the UC group and healthy controls, (v) serum Hcy concentration examination methods, (vi) the quality of each included study (NOS score), and (vii) the serum level of Hcy of each original study.

Quality evaluation of each study

The general quality of the included eighteen studies was evaluated by Newcastle-Ottawa scale (NOS) [13]. The NOS ranges from 0 to 9 stars and the more stars the higher quality of the included case or cohort study.

Statistical analysis

All the data was analyzed by Stata10.0 SE software. The correlation between serum Hcy level and ulcerative colitis was expressed by stand mean difference (SMD). Before pooling the data, we first evaluated the statistical heterogeneity across the included studies by I^2 test ($I^2 > 50\%$, random effect model; $I^2 \leq 50\%$, fixed effect model), and then pooled the SMD by a fixed or random effect model. The publication bias was evaluated through a Begg's funnel plot and Egger's test. Two tails $p < 0.05$ was considered statistical significant.

Figure 1: The publication screen flow chart in the electronic databases.

Results

Main features of the included publications

After systematic searching the related electronic databases, eighteen publications relevant to serum Hcy and UC were finally included in the present meta-analysis. The publication electronic searching procedure is shown in **Figure 1**. The general features of the included eighteen publications are demonstrated in **Table 1**. Sample sizes ranged from 51 to 1063 subjects. The serum Hcy levels ranged from 10.10 to 20.67 $\mu\text{mol/L}$ for UC groups and 6.80 to 13.21 $\mu\text{mol/L}$ for control groups. The NOS score, which was used for evaluation the quality of the case-control studies, ranged from 4 to 6.

2 Serum Hcy concentration in UC and healthy controls

The serum Hcy levels were 14.01 ± 2.76 and 10.31 ± 1.59 $\mu\text{mol/L}$ for UC group and healthy controls respectively. The serum Hcy concentration of UC group was significantly higher than that of controls with statistical difference ($p < 0.05$), **Figure 2**.

Table 1: Main features of the included eighteen publications.

Author (Year)	Region	Sample size		Age		Hcy level($\mu\text{mol/L}$)		Methods	NOS score
		UC	Control	UC	Control	UC	Control		
Danese (2005) [10]	Italy	83	70	NA	NA	11.1 $\pm$ 4.9	7.1 $\pm$ 1.7	HPLC	6
Drzewoski J (2006) [11]	Greece	30	21	50.3 $\pm$ 11.7	53.1 $\pm$ 12.8	10.1 $\pm$ 3.1	6.8 $\pm$ 2.5	HPLC	6
Jiang Y (2010) [14]	China	299	764	NA	NA	20.67 $\pm$ 6.42	13.21 $\pm$ 5.11	Enzymatic cycling method	4
Akbulut S (2010) [15]	Turkey	55	45	47.4 $\pm$ 13.8	46.4 $\pm$ 13.8	13.3 $\pm$ 1.93	11.2 $\pm$ 3.8	HPLC	6
Chen ML (2012) [16]	China	112	110	39.4 $\pm$ 11.7	40.3 $\pm$ 10.8	11.27 $\pm$ 7.26	8.19 $\pm$ 4.81	HPLC	5
Sun J (2012) [17]	China	60	20	NA	NA	14.67 $\pm$ 6.77	11.16 $\pm$ 2.67	Chemiluminescence	5
Ni Z (2013) [18]	China	52	50	47.4 $\pm$ 13.8	46.4 $\pm$ 13.89	13.70 $\pm$ 1.92	11.10 $\pm$ 3.85	Enzymatic cycling method	4
Wang JJ (2014) [19]	China	68	60	45.8 $\pm$ 12.7	NA	14.90 $\pm$ 5.39	11.38 $\pm$ 4.39	Chemiluminescence	4
Liu SL (2014) [20]	China	50	50	46.7 $\pm$ 13.2	46.3 $\pm$ 13.9	13.73 $\pm$ 1.91	11.24 $\pm$ 3.85	Enzymatic cycling method	5
Ju HY (2014) [21]	China	60	60	58.12 $\pm$ 7.49	68.29 $\pm$ 7.33	14.74 $\pm$ 1.91	10.26 $\pm$ 1.48	Enzymatic cycling method	5
Dnauta O (2014) [22]		47	65	37.94 $\pm$ 13.44	34.38 $\pm$ 12.12	10.34 $\pm$ 4.31	9.71 $\pm$ 2.81	fluorescent traceing assay	6
Chen SW (2015) [23]	China	100	100	61.37 $\pm$ 8.24	67.53 $\pm$ 6.87	15.02 $\pm$ 1.70	10.19 $\pm$ 1.53	Enzymatic cycling method	4
Zhou XJ (2015) [24]	China	60	55	47.0 $\pm$ 12.8	49.0 $\pm$ 10.8	18.60 $\pm$ 2.90	10.50 $\pm$ 4.304	Enzymatic cycling method	5
Yang J (2016) [25]	China	64	32	NA	NA	13.78 $\pm$ 1.91	11.16 $\pm$ 1.46	Fluorescence polarization	5
Zhuo XJ (2016) [26]	China	84	30	42.15 $\pm$ 9.84	40.83 $\pm$	14.28 $\pm$ 1.21	11.16 $\pm$ 1.46	Immunoturbidimetry	5
Xue XY (2017) [27]	China	112	100	41.13 $\pm$ 9.14	41.79 $\pm$ 8.95	16.93 $\pm$ 9.49	10.33 $\pm$ 7.48	Enzymatic cycling method	4
Zheng SZ (2017) [28]	China	397	574	41.30 $\pm$ 11.50	40.30 $\pm$ 8.70	11.38 $\pm$ 3.46	9.65 $\pm$ 2.94	Enzymatic cycling method	6
Liu C (2018) [29]	China	63	63	41.7 $\pm$ 6.0	46.6 $\pm$ 6.1	13.74 $\pm$ 1.90	11.23 $\pm$ 3.57	Enzymatic cycling method	4

NOS: Newcastle-Ottawa scale

HPLC: High-performance liquid chromatography

Figure 2: The scatter plot of serum Hcy level distribution of each included publications between UC and controls groups.

Figure 3: Forrest plot of serum Hcy levels between UC patients and healthy controls. The squares and horizontal lines demonstrate the study-specific SMD and 95% CI. The area of the squares reflects the study specific weight. The diamond represents the pooled OR and 95% CI.

3 Meta-analysis

Before pooling the data, we first evaluated the statistical heterogeneity across the included eighteen publications. Significant heterogeneity was found ($I^2=94.5\%, p<0.001$) among the included studies. Therefore, the SMD were pooled through the random effect model. The pooled SMD was 1.20 (95% CI:0.89-1.51) indicating serum Hcy levels were significantly higher in UC group compared to healthy controls with statistical difference ($Z=7.52, P<0.001$), **Figure3**.

Figure 4: Forest plot of SMD by omitting each of the included publications. The circle and horizontal lines demonstrate the study-specific SMD and confidence interval by omitting the corresponding study.

4 Sensitivity analysis

Sensitivity analysis was performed by omitting each of the included publications. The pooled SMD changed from 0.93 (95% CI: 0.86-1.00) to 1.17 (95% CI: 1.09-1.25) by omitting each of the included studies, **Table 2**. This indicates that the pooled SMD were not sensitive to any one of the included studies, **Figure 4**.

Ethical approval: The conducted research is not related to either human or animals use.

5 Publication bias analysis

The publications bias was evaluated by a funnel plot and Egger's line regression test. The funnel plot was asymmetrical at the bottom which demonstrated obvious publication bias (**Figure 5**). However, the Egger's line regression test indicated no publications bias ($t=1.45, p=0.17$).

Discussion

Ulcerative colitis is a chronic nonspecific inflammatory disease of the colon and rectum whose etiology is still unclear [30, 31]. The lesion are usually confined to the mucosa and submucosa of the large intestine. Most lesions are located in the sigmoid colon and rectum, but can also extend to the descending colon or even the whole colon [32, 33]. The course of the disease is long and often recurs. This disease occurs at any age, but the most common

Table 2: Sensitivity analysis of SMD by omitting each of the included publications.

Study omitted	Estimate SMD	95% CI	
		Lower limit	Upper limit
Danese (2005)	1.21	0.88	1.54
Drzewoski J (2006)	1.20	0.88	1.53
Jiang Y (2010)	1.19	0.85	1.54
Akbulut S (2010)	1.22	0.905	1.56
Chen ML (2012)	1.24	0.92	1.57
Sun J (2012)	1.23	0.91	1.56
Ni Z (2013)	1.22	0.89	1.55
Wang JJ (2014)	1.23	0.90	1.56
Liu SL (2014)	1.22	0.90	1.55
Ju HY (2014)	1.12	0.82	1.42
Dnauta (2014)	1.26	0.942	1.58
Chen SW (2015)	1.09	0.82	1.36
Zhou XJ (2015)	1.14	0.83	1.45
Yang J (2016)	1.19	0.86	1.51
Zhuo XJ (2016)	1.13	0.82	1.441
Xue XY (2017)	1.23	0.89	1.561
Zheng SZ (2017)	1.24	0.91	1.58
Liu C (2018)	1.22	0.89	1.551
Combined	1.20	0.89	1.511

Figure 5: Funnel plot of correlation between serum homocysteine levels and ulcerative colitis. The solid dots represent each included study.

is 20-30 years old [34, 35]. The etiology of ulcerative colitis is still unknown. However, most studies believe that psychological factors play an important role in the occurrence and development of ulcerative colitis [36, 37]. Previously publications demonstrated that depression or anxiety was significantly improved after colectomy [38, 39]. Other studies showed that ulcerative colitis is an autoimmune disease [40, 41].

Homocysteine is a non-proteinogenic α -amino acid. It is a homologue of the amino acid cysteine, differing by an additional methylene bridge (-CH₂-). It is biosynthesized from methionine by the removal of its terminal C^ε methyl group. Several studies have discussed the correlation between the serum homocysteine concentration and ulcerative colitis risk, and most of the publication found that the serum homocysteine was elevated in UC patients compared to healthy controls [10, 11]. However, other studies showed there was no statistical difference of serum Hcy concentration between UC groups and healthy controls [22]. Therefore, we performed this meta-analysis by pooling all the published data relevant to serum homocysteine concentration and ulcerative colitis in order to further evaluate their correlations and potential diagnostic performance as serological biomarker.

In the present meta-analysis, we included eighteen case-control studies published from 2005 to 2018. The pooled data indicated that the serum Hcy levels in UC groups were significantly higher than that of healthy controls (14.01 ± 2.76 vs 10.31 ± 1.59 $\mu\text{mol/L}$, $p < 0.05$). This indicates that Hcy may play an important role in UC development and may be used as serological biomarker for UC diagnosis.

However, there were several limitations of the present meta-analysis: (i) significant statistical heterogeneity across the included studies, (ii) only studies published in English or Chinese were screened and included, and (ii) the general quality of the original publications was low.

In conclusion, increased serum Hcy levels were associated with the increased risk of UC. However, all the studies included were case-control studies, which can not reveal the causal relationship between Hcy level and UC. Therefore, more prospective cohort or basic studies relevant to Hcy and UC are needed to further evaluate the their correlation or provide more precise evidence.

Conflict of interest: Authors state no conflict of interest

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