

# Association between Carotid Intima-Media Thickness and Inflammatory Bowel Disease: Systematic Literature Review

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Systematic Review Article

## ABSTRACT

### Background:

Atherosclerosis is involved in inflammatory diseases, and inflammation can be a valuable predictor of cardiovascular disease. On the other hand, an increase in intima-media thickness (IMT) is usually considered as a primary marker of atherosclerotic lesions. Hence, measurement of IMT may be useful for early detection of atherosclerosis in patients with inflammatory bowel disease (IBD). The aim of this study was to systematically review the literature in which the IMT had been evaluated as diagnostic marker for the detection of atherosclerosis in patients with IBD.

### Materials and Methods:

A systematic literature search was performed in PubMed, Scopus, and Google scholar using the following search method ((*inflammatory bowel disease OR IBD OR Crohn's disease OR ulcerative colitis*)) AND (*intima OR intima media thickness OR intimal medial thickness OR IMT OR carotid intima-media thickness OR CIMT*) to evaluate the association between IBD and IMT. After collecting the eligible documents, the desired data were extracted and analyzed.

### Results:

Of total 278 collected documents, only 14 relevant articles with total 1333 participants including 720 patients with IBD and 613 healthy controls were included for data assessment. The results of the articles did not support significant association between IMT and IBD. However, in some studies it was shown that IMT was elevated in patients with IBD.

### Conclusion:

The results of this survey showed that there was no significant difference in IMT between the patients with IBD and healthy control groups; therefore, IMT cannot be considered as a predictor of atherosclerosis and future cardiovascular events in patients with IBD.

**Keywords:** Intimal medial thickness, Carotid intima-media thickness, Inflammatory bowel disease, Crohn's disease, Colitis, ulcerative

*please cite this paper as:*

Rajabzadeh F, Bahari A, Esmailzadeh A, Mosannen Mozaffari H, Goshayeshi L, Soltani M. Association between Carotid Intima-Media Thickness and Inflammatory Bowel Disease: Systematic Literature Review. *Govaresh* 2017;22:106-112.

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Received: 02 Apr. 2017

Edited: 12 Jun. 2017

Accepted: 14 Jun. 2017

## INTRODUCTION

Inflammatory bowel disease (IBD) refers to diseases that cause inflammation of the intestinal wall. Crohn's disease (CD) and ulcerative colitis (UC) are two most important types of IBD, which have similarities in some aspects (1). Although the main etiology remained unknown, but studies indicated that intestinal tissue damage due to an abnormal response of the immune system and multiple involvements of non-immune cells such as microvascular endothelial cells might have a role in the pathogenesis of the

disease (1,2). The incidence of IBD varies in different geographical areas. The incidence of both CD and UC is high in the UK, Europe, and North America (3,4). The annual incidence rate varies from 37 to 246 patients per 100000 for UC and 26 to 199 patients per 100000 for CD (5). The age of onset for UC and CD is generally between 15 to 30 years or between 60 to 80 years. The symptoms depend on the affected area in the gastrointestinal tract. Regarding the etiology of IBD, it is suggested that the stimulation of immune system may cause an inflammatory response in the gastrointestinal tract. New findings suggest that particular genes may be involved in the pathogenesis of IBD. But, findings show that smoking, drug use, and family history of IBD may have an impact on the incidence and progression of the disease (6).

An increase in intima-media thickness (IMT) in carotid artery is usually considered as a primary marker to identify structural changes of atherosclerotic lesions in the arterial wall and the prevalence of cardiovascular disease, particularly myocardial ischemia (7-9). Also, carotid IMT is a strong predictor of future cardiovascular events and a prognostic factor to predict the risk of myocardial infarction and stroke (10). Thus, the increase in IMT of the carotid artery is an important factor in the incidence of stroke and heart attack. So far, several studies have been done on the relationship between carotid IMT and the incidence of various diseases such as stroke, myocardial infarction, and type 1 diabetes mellitus (11,12). Also, by using non-invasive ultrasound method, it is shown that carotid IMT can be considered as a general marker for atherosclerosis.

Recent studies have shown that advanced atherosclerosis may be involved in outbreaks of autoimmune and inflammatory diseases such as systemic lupus erythematosus (SLE), and rheumatoid arthritis (RA) (13). As a result, inflammation can be a cause of cardiovascular disease. Thus, measurement of the IMT of carotid artery in IBD, which is an autoimmune disease with chronic inflammatory state, is thought to be a useful diagnostic method for early detection of atherosclerosis in patients with IBD. The aim of this study was to systematically review the literature wherein the IMT had been evaluated in patients with IBD.

## MATERIALS AND METHODS

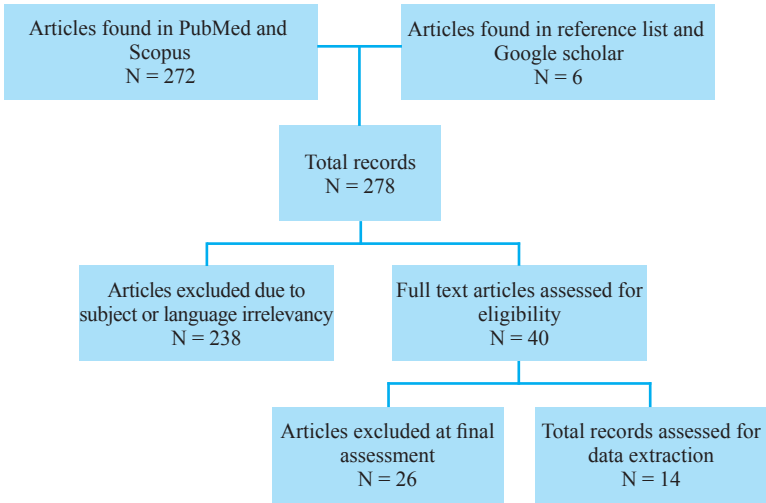
### Literature search strategy

A systematic literature search was performed in PubMed, and Scopus to investigate the IMT in patients with IBD. To perform the literature search in PubMed, "*carotid intima-media thickness*" and "*inflammatory bowel disease*" were searched as key terms in the title, keywords, and abstract of articles using the following search method ((*inflammatory bowel disease OR IBD OR Crohn's disease OR ulcerative colitis*)) AND (*intima OR intima media thickness OR intimal medial thickness OR IMT OR carotid intima-media thickness OR CIMT*). On the other hand, to find potentially relevant articles in Scopus, "*inflammatory bowel disease OR IBD OR Crohn's disease OR ulcerative colitis*" were searched and then "*carotid intima-media thickness OR CIMT*" were searched within the results. Afterwards, the records were limited to only literatures with English language that had been conducted on human. Along with these electronic databases and to include other eligible documents, Google scholar and the reference lists of the previously included documents were also searched.

### Eligibility criteria

To obtain more reliable results and to include all potential documents as much as possible, no strict inclusion criteria were defined. As a result, almost all relevant articles wherein the association between IBD and CIMT had been studied were collected and used for further evaluation. Moreover, no time limitation was defined for the collection of eligible documents. But, the records were limited to only articles with English language. In addition, duplicated documents and articles that reported the same population as well as articles with unavailable or unpublished full texts were excluded from further evaluation. Furthermore, letters and review articles as well as case series were excluded from further assessment. Thus, according to the above-mentioned criteria, the exclusion criteria in this literature review were:

- I. Language other than English
- II. Letters, editorials, case reports, and review articles
- III. documents with subject irrelevancy



**Fig. 1:** Flowchart of the literature search and strategy for the selection of relevant documents.

**Data extraction**

All necessary data including the authors’ names, date of publication, origin of study, and the total number of studied population in the selected documents were extracted. Other informative data including target population, sex ratio, study design, methods of assessment, and measured variables, in addition to the main findings of each study were collected and used for data assessment. All procedures of literature search and study selection, as well as data extraction were performed using the recommendation of modified PRISMA checklist 2009 as an standard protocol for systematic reviews (14). All qualified articles were collected and the desired data were retrieved and used for further conclusion.

**Measured variables**

Carotid IMT measurement had been used for clinical evaluation of the patients, but other methods including aortic intima-media thickness (aIMT), pulse wave velocity (PWV) measurement, brachial artery flow-mediated dilatation (BAFMD), and carotid and vascular ultrasonography were also used for further evaluation of the variables. Clinical and laboratory tests in addition to nutritional assessment had also been performed in some studies. Clinical and laboratory parameters included evaluating serum hemoglobin, plasma homocysteine, insulin levels and insulin resistance, vitamin B12, folate, and serum

lipid profile. Moreover, inflammatory markers such as erythrocyte sedimentation rate (ESR), fibrinogen, and highly sensitive C-reactive protein had been measured as confirmation tests. The variables of interest that had been evaluated in the selected literature included aIMT, cIMT, carotid artery stiffness (CAS), PWV, BAFMD, smoking status, and IBD activity

**RESULT**

**Literature search results**

Of the total 272 documents found through database search, 216 articles were in PubMed, and 56 were in Scopus. Six additional documents were found through reference lists screening and Google scholar search. Of the collected literature, 223 articles were excluded in the first step due to irrelevancy. Additional 20 documents were also excluded after limiting the records to only articles conducted on human. 15 articles were further excluded for language irrelevancy. Moreover, 6 review articles were also excluded from further evaluation. Thus, the full text of 14 appropriate documents wherein the IMT had been evaluated for the detection of subclinical atherosclerosis in patients with IBD were collected and used for further assessment. The process of literature selection is demonstrated in figure 1.

**General information of the included articles**

In the current literature review, 14 articles with

Table 1: General information of the included literature

No	First author	Year	Country	Mean age	Design*	Sex (Male/Female)	Patients number
1	Ozturk K (15)	2015	Turkey	31.66	OS	97/29	126
2	Aloi M (16)	2015	Italy	11.1	CCS	20/14	34
3	Alkan E (17)	2014	Turkey	38.4 ± 6.5	CCS	22/18	40
4	Theocharidou E (18)	2014	Greece	36.1 ± 10.6	CCS	20/22	42
5	Kim KO (19)	2014	Korea	38.5 ± 6.62	RS	26:12	38
6	Akdoğan RA (20)	2013	Turkey	48 ± 15	CSS	21/16	37
7	Principi M (21)	2013	Italy	41 ± 16	PCS	25/24	49
8	Kayahan H (22)	2012	Turkey	34.4 ± 9.8	CSS	21/18	39
9	Aloi M (23)	2012	Italy	15.2	CCS	23/29	52
10	Broide E (24)	2011	Israel	31.46 ± 7.23	CCS	28/22	50
11	Dagli N (25)	2010	Turkey	39.4 + 11	CSS	23/17	40
12	Maharshak N (26)	2007	Israel	36 ± 11	CSS	28/33	61
13	Van Leuven SI (27)	2007	Netherlands	42.4 ± 12.8	CSS	27/33	60
14	Papa A (28)	2006	Italy	34 ± 10.2	CSS	34/18	52
* CCS: Case-control study, CSS: Cross-sectional study, OS: Observational study, PCS: Prospective cohort study, RS: Retrospective study						Male: 415 Female: 305	Total: 720

total of 1333 participants including 720 patients with IBD and 613 healthy controls were studied. The patients with IBD included 362 patients with CD and 266 patients with UC. In addition, the types of the disease were identified in two studies with 92 patients. The number of studied patients with IBD ranged from 34 to 126 in the included documents, among which 415 were male and 305 were female patients. The age of the patients also varied from 5 to 60 years. The oldest and the most recent articles among the collected documents had been published in 2005 and 2015, respectively, indicating that few studies had been conducted so far to evaluate the role of IMT as a diagnostic tool for the detection of atherosclerosis in patients with IBD. Of the collected documents, five were case-control, and six were cross-sectional studies. In addition, there were one observational, one retrospective, and one prospective cohort study. General information of the included documents is demonstrated in table 1.

Study findings

Comparison of the reported IMT between the patients and control groups showed that IMT increased in patients with IBD. In only three studies with overall 122 patients it was also shown that there were significant differences between the patients with IBD and control

groups regarding the values of PWV, and cIMT (17,18,20). Carotid and vascular ultrasonography and BAFMD assessments also showed that cIMT, PWV, and C reactive protein were significantly higher in patients with UC, while BAFMD values were lower in patients with IBD (20). Moreover, findings demonstrated that patients with IBD were at increased risk of endothelial dysfunction and atherosclerosis (21). Carotid artery stiffness was also impaired in the patients groups. Biochemical tests and evaluation of inflammatory markers showed that plasma homocysteine, C reactive protein, ESR, and fibrinogen levels were significantly higher in patients with IBD (25).

On the other hand, the results of studies with overall 425 study population showed that although cIMT was higher in patients with IBD, the difference between the patients and healthy controls was not significant (16,19,22,24,26). Also, findings demonstrated that aIMT could be considered as an earlier marker of atherosclerosis compared with cIMT in patients with active IBD (16). In table 2, the methods of assessment, measured variables, and main findings of each study are summarized.

DISCUSSION

Atherosclerosis is a chronic inflammatory disease, which is considered as the main cause of heart

Table 2: Methods of assessment, sources of sampling, and main findings of the included literature

No	First author	Methods ®	Variables *	Main findings *
1	Ozturk K	CU	PWV, BAFMD, cIMT	Patients with IBD have increased risk of endothelial dysfunction and atherosclerosis.
2	Aloi M	LT, CU	aIMT, cIMT, IBDA, Inflammatory markers	aIMT is an earlier marker of preclinical atherosclerosis than cIMT in young children with active IBD.
3	Alkan E	CU	cIMT, PWV	IBD patients have an increased risk of subclinical atherosclerosis as shown by greater values of cIMT and PWV.
4	Theocharidou E	CU, ME	cIMT, IBDA	IBD is a predictor of cIMT and there is an association between early arterial wall alterations and IBD.
5	Kim KO	LT, CU	cIMT	c-IMT as a marker for early atherosclerosis did not increase in patients with IBD.
6	Akdoğan RA	VU	cIMT, PWV	cIMT was significantly higher in patients with ulcerative colitis.
7	Principi M	LT, VU	BAFMD, cIMT	Patients with IBD might be at higher risk for atherosclerosis.
8	Kayahan H	CU, LT	cIMT, BAFMD, serum lipids, and smoking status	Functional atherosclerosis is present in IBD before early structural changes occur in vasculature.
9	Aloi M	CU	cIMT	IBD is an independent risk factor for atherosclerosis.
10	Broide E	NM, CU, LT	cIMT, CRP, and homocysteine	Patients with Crohn's disease are not at risk for developing early atherosclerosis.
11	Dagli N	LT, CU	cIMT, CAS, folate, Homocysteine, vitamin B12	Patients with IBD are at risk of early atherosclerosis as shown by greater values of cIMT, and carotid artery stiffness.
12	Maharshak N	LT, CU	cIMT, Inflammatory markers	IBD appears not to be a risk factor for accelerated atherosclerosis.
13	Van Leuven SI	LT, CU	cIMT	Patients with Crohn's disease have increased IMT, indicative of accelerated atherogenesis.
14	Papa A	CU, LT	cIMT, CRP, and homocysteine	IBD patients have an increased risk of early atherosclerosis.

® LT: Laboratory tests, VU: Vascular ultrasound, CU: Carotid ultrasonography, ME: Medical examination, NM: Nutritional assessment,

\* BAFMD: Brachial artery flow-mediated vasodilatation, PWV: Pulse wave velocity, aIMT: Aortic intima-media thickness, cIMT: carotid intima-media thickness, CAS: Carotid artery stiffness, IBD: Inflammatory bowel disease, IBDA: Inflammatory bowel diseases activity, CRP: C-reactive protein

attacks, and strokes (29). Therefore, identification of markers for early diagnosis of atherosclerosis, especially in patients with IBD will be of great importance. Epidemiological studies have shown that a c-IMT  $\geq 1$  mm can correlate with increased risk of atherosclerosis and cardiovascular events (30). Clinical data demonstrated that the prevalence of heart failure was rather high in patients with increased IMT (31). IMT measurement, which is a widely used diagnostic marker in atherosclerosis and vascular disease, may also be helpful to prevent future cardiovascular disease. It is shown that induction of immune response may lead to IBD, and since inflammation has also been shown to be associated with cardiovascular disease, IMT as a predictor of cardiovascular disease and atherosclerosis may show the involvement of the vascular structural changes in patients with IBD (32,33). Since endothelial dysfunction is the first structural and functional manifestation of

atherosclerotic cardiovascular disease; therefore, it is probable that IMT may help to predict the early onset of atherosclerosis, particularly in patients with IBD.

Findings show that IMT is significantly higher in patients with IBD (27,28). The results of studies also showed that cIMT was significantly increased in patients with CD compared with healthy volunteers (0.71 mm in patients vs. 0.59 mm in controls) (16,27). Since cIMT value is greater in patients with IBD; thus, it is expected that these patients may be at increased risk of atherosclerosis compared with healthy individuals. The results also indicated that since a significant association existed between early arterial wall alterations and the onset of IBD, IBD can be considered as a predictor of cIMT (18). On the other hand, the results of some studies showed that IMT was similar between the patients with IBD and healthy controls, indicating that IBD is not considered as a risk factor for developing accelerated atherosclerosis



(22,26). Moreover, IMT is shown to be associated with several biochemical parameters including homocysteine, but no significant association has been found between IMT and inflammatory markers such as high-sensitivity C-reactive protein in patients with chronic kidney disease (34).

The results of this study showed that IMT was similar between the patients with IBD and healthy controls. Therefore, it cannot be considered as an indicator of atherosclerosis and future cardiovascular disease in patients with IBD. Hence, no significant correlation was found between IBD and IMT, indicating that patients with IBD may not be at increased risk of thrombotic complications. However, these results may be due to homogeneity of studied population, since almost two third of the studied patients (469 of 720) were from two countries (Turkey, n = 282; and Italy, n = 187). Despite these conflicting results, it has been shown that chronic inflammatory

disease such as IBD is a risk factor for accelerated atherogenesis and future cardiovascular events. But, to prove such an association, prospective, long-term, multicenter cohort studies are required.

## CONCLUSION

The results of this study showed that no significant difference existed in IMT including aIMT and cIMT between the patients with IBD and control groups. Therefore, these markers cannot be considered as predictors of atherosclerosis and future cardiovascular events in patients with IBD. Further studies are required to prove possible association between IMT and IBD.

## CONFLICT OF INTEREST

The authors declare no conflict of interests related to this work.

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