Inflammatory and Lipid-Associated Markers of Cardiovascular Diseases in Children with First Exacerbation of Inflammatory Bowel Disease

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Background: Adult patients with inflammatory bowel disease (IBD) are at increased risk of early atherosclerosis and atherosclerosis-driven cardiovascular diseases. However, data on the development of early, subclinical atherosclerosis in children with IBD are scarce. The aim of this study was to assess selected biomarkers of atherosclerosis in children with IBD.

Material/Methods: The study group comprised 30 children with first exacerbation of IBD. Twenty healthy children were enrolled into the control group. Total cholesterol, triglycerides, low-density lipoproteins (LDL), high-density lipoproteins (HDL), lipoprotein (a) (Lp(a)), interleukin 6 (IL-6), high sensitivity C-reactive protein (hs-CRP), and oxidized LDL (ox LDL) were determined.

Results: There were no significant differences in lipids profiles in IBD children and controls. Mean IL-6 level (8.996 pg/ml) was significantly higher in the IBD group compared to controls (3.502 pg/ml). Mean hs-CRP concentration was significantly higher in IBD children than in controls (7.648 and 1.290 µg/ml, respectively). In the IBD group, mean ox-LDL concentration (144.837 ng/ml) was lower than in controls (162.352 ng/ml), but the difference was non-significant (P=0.4). Mean Lp(a) serum level was higher in patients with IBD (19.418 mg/dl) than in controls (10.970 mg/dl), but it was also non-significant.

Conclusions: No significant differences were found in biomarkers of atherosclerosis in children with IBD compared to controls. Elevated IL-6 and hs-CRP level are well-established inflammatory markers. Further studies are needed to fully determine cardiovascular risk factors in IBD children.

MeSH Keywords: Atherosclerosis • Colitis, Ulcerative • Crohn Disease • Inflammatory Bowel Diseases

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Background

Atherosclerosis is a chronic, progressive disease characterized by the accumulation of lipids and fibrous elements in the medium and large arteries. It is initiated by endothelial denuding injury leading to the proliferation of smooth muscle cells in the arterial intima and increased production of extracellular macromolecules [1].

There is abundant scientific evidence indicating the pivotal role of inflammation in every stage of atherosclerosis, including initiation, evolution, and thrombotic complications. Moreover, patients with chronic inflammatory diseases, such as rheumatoid arthritis, psoriasis, or systemic lupus erythematosus, are at increased risk of accelerated atherosclerosis and cardiovascular disorders [2–4]. There is ongoing debate concerning the association between other chronic immune-mediated inflammatory disorders, such as inflammatory bowel disease (IBD), and atherosclerosis.

Inflammatory bowel disease is a chronic, relapsing-remitting, immune-mediated disorder of the gastrointestinal tract, which includes Crohn’s disease, ulcerative colitis, and IBD-unclassified. Although the etiology of IBD remains unclear, several pathogenic factors have been proposed, including aberrations in multiple susceptibility genes, variations in the luminal microbiota, environmental triggers, and aberrant immunoregulation [5]. Moreover, mesenteric microvascular thrombosis was identified in altered perfusion, inflammation, and tissue injury in IBD [6]. Thus, it has been described as another plausible pathogenic factor in IBD. A recent experimental study revealed another potential pathogenic factor of IBD; Kim et al. found that in vitro, the administration of 4-nonylphenol up-regulates proinflammatory genes and decreases the expression of the anti-inflammatory genes in human cells lines, promoting gastrointestinal tract inflammation [7].

Increased risk of deep venous thrombosis and pulmonary embolism has been shown in IBD patients [8]. Clinical studies have revealed that the incidence of systemic thromboembolic complications in adults with IBD ranges between 1% and 7.7% [9]. Although the link between venous thromboembolic events and IBD is well-established, the risk of arterial thromboembolic events, such as ischemic heart disease or cerebrovascular events, in IBD patients is controversial. While some reports indicate that patients with IBD are at increased risk of early atherosclerosis and atherosclerosis-driven cardiovascular diseases [9–12], several studies do not support these findings [13–15].

In addition, most relevant studies have been carried out in adults, but atherogenesis originates in early stages of life and may remain asymptomatic for decades. Thus, studies on the identification of early, subclinical atherosclerosis in children with IBD are required.

Several groups of atherosclerosis biomarkers have been proposed for diagnostic use: inflammatory markers (e.g., high-sensitivity C-reactive protein, interleukin 6, and CD40L); lipid-associated markers (e.g., low-density lipoproteins, high-density lipoproteins, oxidized low-density lipoproteins, triglycerides, and lipoprotein (a)); markers of endothelial dysfunction (e.g., nitric oxide, asymmetric dimethylarginine, soluble vascular adhesion molecules, von Willebrand factor, and endothelial progenitor cells); oxidative stress (e.g., neutrophil myeloperoxidase); markers of neovascularization (e.g., placental growth factor and stromal-derived factor 1); and genetic markers (e.g., polymorphism within low-density lipoprotein receptor gene, apolipoprotein B gene, CYP7A1 gene, and transforming growth factor beta 1 gene) [16].

The aim of our study was to assess selected biomarkers of atherosclerosis in children with IBD.

Material and Methods

A total of 30 children hospitalized at the Department of Pediatrics, Medical University of Lublin, Poland, with their first exacerbation of IBD, were recruited to the study. The diagnosis of IBD was based on clinical presentation, endoscopy, and histology according to the Porto criteria [17]. Twenty healthy children were enrolled into the control group.

Blood samples were collected after overnight fasting for the laboratory tests. The following parameters were determined: total cholesterol (T-Chol), triglycerides (TG), low-density lipoproteins (LDL), high-density lipoproteins (HDL), lipoprotein (a) (Lp(a)), interleukin 6 (IL-6), high-sensitivity CRP (hs-CRP), and oxidized LDL (ox-LDL). Plasma lipid levels were determined by the colorimetric enzymatic method (Cormay). The measurement of hs-CRP (Immundiagnostic AG), IL-6 (GennProbe Diaclove SAS), Lp (a) (IBL International GMBH), and ox-LDL (Immundiagnostic AG) were performed using commercially available ELISA kits.

Statistical analysis was carried out using Statistica 10 software. Results are presented as mean ± standard deviation. Comparison between groups was performed by using a Mann-Whitney U-rank test for quantitative variables without normal distribution and Student’s t-test for quantitative variables with normal distribution. Results were considered statistically significant at P<0.05.

Written informed consent was provided by parents and also by the patient in the case of a child aged ≥16 years. The study was approved by the Bioethics Committee at the Medical University of Lublin (KE-0254/25/2013).
The study group comprised 30 children with IBD, including 16 (53%) with ulcerative colitis and 14 (47%) with Crohn’s disease. All subjects were experiencing their first exacerbation of the IBD and were treatment-naive. There were 16 (53%) boys and 14 (47%) girls. The mean age of patients was 13±2.7 years and ranged from 5.5 to 17.5 years. The mean Cole’s index was 95.6±18.2%. According to Cole’s index, 16 (53.3%) children had normal nutritional status, 4 (13.3%) were undernourished, 5 (16.7%) were cachectic, and 5 (16.7%) were overnourished.

Among the children with ulcerative colitis, there were 11 (69%) girls and 5 (31%) boys, with mean age 12.8±2.7 years. The mean Cole’s index was 101.3±18.3%. The majority of patients (12; 75%) presented with pancolitis, 2 (12.5%) with proctitis, and 2 (12.5%) with left-sided colitis. The mean severity index according to Truelove and Witts modified by Ryżko and Woynarowski was 5.2±2.6 points.

Among the children with Crohn’s disease, there were 11 (79%) boys and 3 (21%) girls, with mean age 13±2.3 years. The mean Cole’s index was 90±16.9%. Crohn’s disease affected the terminal ileum and colon in 4 (28.5%); the ileocecal region in 3 (21.5%); the upper gastrointestinal tract, terminal ileum, and colon in 3 (21.5%); only the colon in 3 (21.5%); and the upper gastrointestinal tract and ileocecal region in 1 (7%) child. The mean Pediatric Crohn’s Disease Activity Index was 33.5±16 points.

There were no statistically significant differences in age and Cole’s index between children with ulcerative colitis and those with Crohn’s disease.

Twenty healthy children aged between 5 and 18 (mean 12.5±3.6) years, including 11 (55%) girls and 9 (45%) boys, were in the control group.

|                      | IBD children n=30 | Healthy controls n=20 | P  |
|----------------------|-------------------|-----------------------|----|
| T-Chol, mg/dl        | 131.4±25.60       | 123.6±28.04           | 0.3|
| HDL, mg/dl           | 45.06±13.63       | 40.94±9.1             | 0.4|
| LDL, mg/dl           | 76.77±20.53       | 75.65±23.81           | 0.9|
| TG, mg/dl            | 86.10±32.65       | 71.40±26.48           | 0.1|
| hs-CRP, µg/ml        | 7.648±6.84        | 1.29±1.44             | 0.0|
| II-6, pg/ml          | 8.996±11.83       | 3.502±9.28            | 0.0|
| Lp (a), mg/ml        | 19.418±19.52      | 10.97±9.92            | 0.4|
| ox-LDL, ng/ml        | 144.837±140.79    | 162.35±160.96         | 0.4|

Data are presented as mean ± standard deviation. A P value of <0.05 is considered statistically significant. HDL – high density lipoprotein; hs-CRP – high sensitivity C-reactive protein; IBD – inflammatory bowel disease; II-6 – interleukin 6; Lp (a) – lipoprotein a; LDL – low density lipoprotein; M – mean; ox-LDL – oxidized low density lipoprotein; SD – standard deviation T-Chol – total cholesterol; TG – triglyceride.

### Results

The study group comprised 30 children with IBD, including 16 (53%) with ulcerative colitis and 14 (47%) with Crohn’s disease. All subjects were experiencing their first exacerbation of the IBD and were treatment-naive. There were 16 (53%) boys and 14 (47%) girls. The mean age of patients was 13±2.7 years and ranged from 5.5 to 17.5 years. The mean Cole’s index was 95.6±18.2%. According to Cole’s index, 16 (53.3%) children had normal nutritional status, 4 (13.3%) were undernourished, 5 (16.7%) were cachectic, and 5 (16.7%) were overnourished.

Among the children with ulcerative colitis, there were 11 (69%) girls and 5 (31%) boys, with mean age 12.8±2.7 years. The mean Cole’s index was 101.3±18.3%. The majority of patients (12; 75%) presented with pancolitis, 2 (12.5%) with proctitis, and 2 (12.5%) with left-sided colitis. The mean severity index according to Truelove and Witts modified by Ryżko and Woynarowski was 5.2±2.6 points.

Among the children with Crohn’s disease, there were 11 (79%) boys and 3 (21%) girls, with mean age 13±2.3 years. The mean Cole’s index was 90±16.9%. Crohn’s disease affected the terminal ileum and colon in 4 (28.5%); the ileocecal region in 3 (21.5%); the upper gastrointestinal tract, terminal ileum, and colon in 3 (21.5%); only the colon in 3 (21.5%); and the upper gastrointestinal tract and ileocecal region in 1 (7%) child. The mean Pediatric Crohn’s Disease Activity Index was 33.5±16 points.

There were no statistically significant differences in age and Cole’s index between children with ulcerative colitis and those with Crohn’s disease.

### Discussion

The traditional view regarded atherosclerosis as a localized lipid storage disease leading to flow-limiting arterial stenosis [18]. However, the understanding of atherosclerosis has undergone a remarkable evolution. Atherosclerosis is now considered a chronic inflammatory process of the arterial...
with an autoimmune component resulting from the interplay of lipid metabolism imbalance, maladaptive immune response, and genetic alterations [18–20]. As the fundamental role of inflammation in all stages of atherogenesis has been established, markers of inflammation and endothelial activation may become useful indices of early atherosclerosis and predictors of outcomes, in addition to those provided by traditional risk factors [21].

It is well-established that the initial step in atherogenesis is endothelial injury. The term “endothelial dysfunction” refers to decreased production or availability of the key endothelium-derived relaxing factor – nitric oxide – and increase of contractility, leading to vasoconstriction [21].

Traditional atherosclerotic risk factors, including hypercholesterolemia, hypertension, and diabetes, promotes inflammatory cascade and endothelial damage. Hypercholesterolemia induces adhesion of blood leukocytes to the endothelium [22]. Increased C-reactive protein reduces production and bioavailability of nitric oxide, which in turn inhibits angiogenesis [23]. Oxidized low-density lipoprotein promotes vasoconstriction by decreasing biological activity of endothelium-derived nitric oxide, which in turn inhibits angiogenesis [23].

Table 2. Comparison of the laboratory parameters of children with Crohn’s disease, ulcerative colitis and healthy controls.

|                     | CD patients   | UC patients   | Healthy controls | P-values    |
|---------------------|---------------|---------------|------------------|-------------|
|                     | n=16 M±SD     | n=14 M±SD     | n=20 M±SD        | CD vs. UC   | CD vs. controls | UC vs. controls |
| T-Chol, mg/dl       | 127.69±25.36  | 134.43±26.21  | 123.65±28.04     | 0.4         | 0.7             | 0.4             |
| HDL, mg/dl          | 42.83±14.99   | 47.25±12.68   | 40.94±9.1        | 0.3         | 0.9             | 0.2             |
| LDL, mg/dl          | 73.86±21.58   | 79.76±20.11   | 75.65±23.81      | 0.5         | 0.9             | 0.6             |
| TG, mg/dl           | 95±42.36      | 78.88±20.75   | 71.40±26.48      | 0.5         | 0.2             | 0.4             |
| hs-CRP, µg/ml       | 11.60±5.98    | 4.19±5.66     | 1.29±1.44        | 0.0         | 0.0             | 0.1             |
| II-6, pg/ml         | 14.86±15.00   | 3.87±3.88     | 3.50±9.28        | 0.0         | 0.0             | 0.0             |
| Lp (a), mg/ml       | 20.08±19.54   | 18.83±20.14   | 10.97±9.92       | 0.7         | 0.3             | 0.5             |
| ox-LDL, ng/ml       | 157.20±155.51 | 134.02±130.75 | 162.35±160.96    | 0.9         | 0.8             | 0.3             |

Data are presented as mean ± standard deviation. A P value of <0.05 is considered statistically significant. HDL – high density lipoprotein; hs-CRP – high sensitivity C-reactive protein; IBD – inflammatory bowel disease; II-6 – interleukin 6; Lp (a) – lipoprotein a; LDL – low density lipoprotein; M – mean; ox-LDL – oxidized low density lipoprotein; SD – standard deviation T-Chol – total cholesterol; TG – triglyceride.

Dyslipidemia is one of the most important risk factors of atherosclerosis. Pro-atherogenic lipid profile is defined as elevation in total plasma cholesterol, low-density lipoprotein and triglycerides, and a decrease in high-density lipoprotein [25]. Recent studies indicate that patients with IBD, particularly those with Crohn’s disease, exhibit lower levels of total plasma cholesterol and low-density lipoprotein compared to healthy controls [26,27]. No significant alterations have been found in IBD patients in triglycerides and high-density lipoprotein level in a study performed by Aloi et al. [26]. However, Levy et al. found significantly higher levels of triglycerides in children with Crohn’s disease compared to controls [27]. The pathophysiology of hypcholesterolemia in IBD patients is not clear; it may be linked to systemic inflammation, malabsorption, or malnutrition. Several inflammatory mediators may alter lipid metabolism in IBD. Interleukin-6 and C-reactive protein inhibit adipocyte lipoprotein lipase activity. Tumor necrosis factor-α stimulates lipolysis and hepatic triglyceride synthesis, and decreases adipocyte lipoprotein lipase activity [28]. In patients with IBD, especially Crohn’s disease, the distal ileum, which is responsible for bile acid absorption, is involved in the inflammatory process. Thus, the intestinal malabsorption leading to the loss of bile acids and cholesterol in the stool may be also responsible for alterations in lipid levels in patients with IBD [25]. Contrary to expectations, our study did not reveal any significant differences in lipid levels between children with IBD and healthy controls. These results are consistent with those of Aloi et al., who also found no significant differences in lipid levels between children with IBD and a control group [10]. Relatively short disease duration, mild and moderate activity of inflammation, and normal nutritional status in most of the
patients may explain the lack of significant alterations in lipid profile in our study population.

Oxidatively modified low-density lipoprotein plays a critical role in several stages of atherogenesis, including endothelial injury, activation and dysfunction of endothelial cells, formation of foam cells, and proliferation and migration of smooth muscle cells [24,29]. Grip et al. showed increased plasma level of oxidized low-density lipoprotein in a small group of adults with IBD, reflecting the increased oxidative stress and higher risk of atherosclerosis [29]. In our study, no differences in ox-LDL were observed between IBD children and controls. However, these data must be interpreted with caution. We presume that the lack of a significant increase in ox-LDL results from the young age of the studied patients and the short disease duration.

Lipoprotein (a) is a well-established independent risk factor for atherosclerosis and thrombosis in adults. Koutoubakis et al. found increased levels of lipoprotein (a) in patients with Crohn’s disease, but not in ulcerative colitis patients, compared to healthy controls. Moreover, lipoprotein (a) was significantly higher in active Crohn’s disease compared to non-active Crohn’s disease patients [30]. We did not observe alterations in lipoprotein (a) in IBD children compared to healthy children.

Increased inflammatory markers, such as high-sensitivity CRP and IL-6 in healthy adults, are predictors of the risk of cardiovascular events [22]. On the other hand, CRP and IL-6 are clinical markers of inflammation in IBD. Thus, in patients with chronic inflammatory conditions such as IBD, it is not possible to establish whether the elevation of inflammatory markers is connected with atherogenesis and increased risk of cardiovascular events. In the present study, the level of IL-6 was significantly increased in both Crohn’s disease and ulcerative colitis patients compared to controls, while hs-CRP was significantly elevated solely in Crohn’s disease patients. IL-6 and hs-CRP were significantly higher in children with Crohn’s disease than in children with ulcerative colitis.

A recent meta-analysis showed that IBD is associated with a modest increase of the risk of cerebrovascular accidents and ischemic heart disease, particularly in women and patients younger than 40–50 years [31]. In children with IBD, Aloi et al. evaluated carotid intima media thickness and brachial flow-mediated dilation, and found subclinical structural and functional endothelial dysfunction, suggesting that premature atherosclerosis can occur in children with IBD. Moreover, traditional risk factors of atherosclerosis, except for passive smoking, have no serious effects on children with IBD [10].

Conclusions

Our study found no significant differences in lipid profile and lipoproteins composition in children experiencing the first exacerbation of IBD compared to controls. However, due to the small sample size and relatively short disease duration, our results must be interpreted with caution, as the findings cannot be extrapolated to the whole population of children with IBD. Further long-term prospective studies are needed to monitor lipid and lipoprotein profiles with ultrasonographic markers for subclinical atherosclerosis in children with IBD.

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