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Hyperhomocysteinemia and Crohn's disease in Algeria people

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Dedication

قلبي مدين بأنهار من الشكر والامتنان رياح الامتنان تهب على مراكب الحياة، توجهها نحو مرافئ السعادة، قافلة الشكر تسير عبر صحاري الحياة، تحمل في قلبها كنوز الامتنان.

لتكون بدايتها إلى والدي الحنونين: شكراً لكما على الحب الذي لا يُضاهى والدعم اللا محدود خلال رحلتي الدراسية. هذه المذكرة تخرج بفضلكما وبتضحياتكما. أدعو الله أن يمنحكما الصحة والسعادة دائمًا.

ولأختي العزيزة، هذه المذكرة تخرج لك، إشارة إلى الشغف والإصرار الذي أبديته خلال رحلتك الدراسية. وكذألك إلى أصدقائي الأوفياء. إلى من كانوا مصدرًا للأمل والطاقة

الإيجابية، إلى من زرعوا فيَّ القيم والمبادئ، وساعدوني على تخطي الصعاب والوقوف على قدمي بثبات خالاتي لقد كنتم ولا زلتم مصدرًا للفخر والإلهام، وأتمنى أن يكون هذا العمل شكرًا بسيطًا يعبر عن مدى امتناني لكم وكذألك إلى أصدقائي الأوفياء، لقد كانت رحلتي الدراسية أكثر متعة وإشراقًا بوجودكم إلى جانبي. شكرًا لكم على كل اللحظات الرائعة والدعم الذي قدمتموه.

لقد كانت رحلتي الدراسية أكثر متعة وإشراقًا بوجودكم إلى جانبي. شكرًا لكم على كل اللحظات الرائعة والدعم الذي قدمتموه.

أتمنى لكم جميعًا النجاح والسعادة في المستقبل وإلى كل من ساهم في إتمام هذه المذكرة بنجاح، أريد أن أعبر عن شكري العميق على جهودكم ودعمكم. بفضلكم، تمكنت من تحقيق هذا الإنجاز. أتمنى لكم جميعًا الخير والنجاح في حياتكم الشخصية والمهنية.

أتمنى أن تكون هذه الكلمات كسحابة صيفية، تمطر عليك بغيث من السعادة والتوفيق في كل ركن من ركني حياتك

Dedication

إلى روح جدي " عبد المجيد سعيدة" وجدتي" الشبهة فرحي"، الذين رحلوا عن دنيانا ولكنهم يعيشون في قلوبنا وذاكرتنا دائماً، اللذين علماني معنى الحب والإصرار، أمام ذكراكما أقف بكل خشوع، تملؤنا مشاعر الحب والامتنان. لقد علمتماني معنى القوة والصبر، وغرستما فيّ بذور الحكمة والمحبة. كان وجودكما في حياتي نورًا يضيء دروبي، وعبق حكاياتكما يرافقني في كل خطوة. رحمكما الله وأسكنكما فسيح جناته.

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List of abbreviations

5-MTHF	Methyl group from 5-methyltetrahydrofolate
ATG16L1	Autophagy-related 16-like 1 gene
C/EBPβ	CCAAT/enhancer-binding protein beta
C/EBPδ	CCAAT/enhancer-binding protein delta
C1q	The complement component 1q
C2H5FH4	Methylene tetrahydrofolate
C3a	Complement component 3a
C3b	Complement component 3b
C4a	Complement component 4a
C4b	Complement component 4b
C5	Complement component 5
C9	Complement component 9
CAM	Cellular adhesion molecule
CBS	Cystathionine beta synthase
CD4+	Cluster of differentiation 4-positive
CD8+	Cluster of differentiation 8-positive
CH3FH4	Methyl tetrahydrofolate
CRP	C-reactive protein
CX3CR1	C-X3-C Motif chemokine receptor 1
Cys	Cysteine

CβS	Cystathionine beta synthase
E-cadherin	Epithelial cadherin
ECCO	The european crohn's and colitis organization.
eNOS	Endothelial nitric oxide synthase
FcγR	Fc gamma receptor I
FcγRIIa	Fc gamma receptor IIa
FH4	Tetrahydrofolate
G	Goblet cells
GI	The gastrointestinal tract
Glu-81	The amino acid glutamate (Glu) located at position 81
H2S	Hydrogen sulfide
Hcy	Homocysteine
HHcy	Hyperhomocysteinemia
IBD	Inflammatory bowel diseases
IFNg	Interferon gamma
IGG	Immunoglobulin G
IL	Interleukin
IL-1	Interleukin
IL-12	Interleukin
IL-13	Interleukin
IL-18	Interleukin
IL-1β	Interleukin-1 beta
IL-4	Interleukin

IL-5 Interleukin

IL-6 Interleukin

IL-8 Interleukin

IL-9 Interleukin (specific)

LDL Low-density lipoprotein

Met Methionine

MS Methionine synthase

MTHFR Methylene tetrahydrofolate reductase

Muc2 Mucin 2

NK-T Natural killer T cell

NO Nitric oxide

NOD2 Nucleotide-binding oligomerization domain containing protein 2

O2 Oxygen

PC Paneth cells

Phe-66 The amino acid phenylalanine (Phe) located at position 66

PU.1 The purine-rich box 1

RELMb Resistin-like molecule b proteins

SAH S-adenosyl homocysteine

SAM S-adenosyl methionine

SCFA Short chain fatty acids

TGFβ Tumor growth factor beta

Th Helper cell

TNF Tumor necrosis factor

T-reg	Regulatory T cell
UC	Ulcerative colitis
WHO	World health organization.

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Introduction

Introduction

Inflammatory bowel disease (IBD) is a chronic inflammatory disease of the gastrointestinal tract and is divided into Crohn disease and ulcerative colitis. It occurs in genetically susceptible individuals after an exaggerated immune response to a normal stimulus, such as food and intestinal flora (McDowell et al., 2023), and affects 6.8 million people worldwide (Kudelka et al., 2020).

Dysbiosis disrupts the intestinal barrier by transferring bacterial symbionts into the intestinal mucosa, initiating an aberrant immune response, resulting in an imbalance between pro- and anti-inflammatory molecules (Upadhyay et al., 2023).

Homocysteine is an amino acid not supplied by the diet that can be converted into cysteine or recycled into methionine, an essential amino acid, with the aid of specific B vitamins (Veeranki et al., 2017).

Elevated levels of plasma homocysteine (Hcy) called hyperhomocysteinemia (HHcy) have been implicated in inflammation and remodelling in intestinal vasculature, and HHcy is also known to aggravate the pathogenesis of inflammatory bowel disease (IBD). Interestingly, colon is the pivotal site that regulates Hcy levels in the plasma (Givvimani et al., 2012).

For instance, the C-reactive protein (CRP) is one of the proteins produced by hepatocytes during the acute phase reaction, mainly by stimulation with interleukin (IL)-6, and is a serum biomarker widely used in various inflammatory diseases (Wagatsuma et al., 2021).

Anemia defined as reduction in hemoglobin (Hb), is a common extraintestinal manifestation of inflammatory bowel disease (IBD) and is frequently overlooked as a complication. Patients with IBD are commonly found to have iron deficiency anemia (IDA) secondary to chronic blood loss (Kaitha et al., 2015).

This research study presented some objectives cited below:

- Evaluation of epidemiological research study.
- Measurement of homocysteine, CRP and hemoglobin.
- Morphological and histological study in patients infected with Crohn’s disease in Constantine and Tebessa.

CHAPTER I

Hyperhomocysteinemia

I. Hyperhomocysteinemia

I.1. Definition of homocysteine

Homocysteine (Hcy) is a sulfur containing amino acid formed during the metabolism of methionine (Met) to cysteine (Cys) with the chemical formula C4H9NO2S (Kumar et al., 2017) (Figure 2).

Homocysteine is not present in naturally occurring proteins, but is an important metabolic branch point in the pathway from methionine to cysteine (Dempster et al., 2020).

Homocysteine levels can be increased by different conditions including genetic factors, diet, life style, several medications (Hermann and Sitdikova., 2021).

Homocysteine levels vary between men and women, with a normal range typically between 5 to 15 micromole/L (Veeranki et al., 2017).

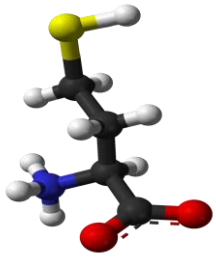

Figure 1. A 3-D model of homocysteine (Samanthi, 2018).

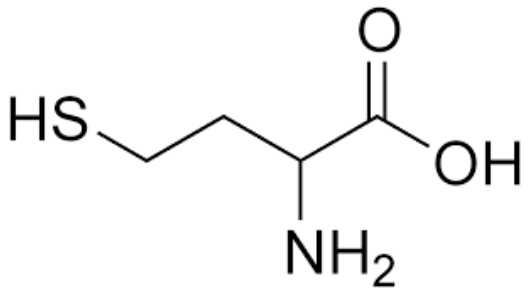

Figure 2. Homocysteine structure (Ganguly and Alam, 2015).

I.2. Biosynthesis and metabolism of homocysteine

2.1. Biosynthesis

Homocysteine is synthesized in the body through a series of biochemical reactions known as the methionine cycle. Methionine, an essential amino acid obtained from dietary sources, serves as the precursor for homocysteine biosynthesis (Mohameed, 2016; and Bhargava, 2018) (Figure 3).

The conversion of methionine to S-adenosyl methionine (SAM) is a key step in this process, facilitated by the enzyme methionine adenosyl transferase (Figure 3). SAM acts as a methyl donor in various methylation reactions throughout the body. During these reactions, SAM donates a methyl group and is transformed into S-adenosyl homocysteine (SAH). SAH is then enzymatically hydrolysed by SAH hydrolase to yield homocysteine (Mohameed, 2016; and Bhargava, 2018).

2.2. Metabolism

The remethylation process and the transculturation pathway are the two primary pathways involved in homocysteine metabolism (Bhargava, 2018).

In the remethylation pathway, homocysteine is converted back to methionine through the transfer of a methyl group from 5-methyltetrahydrofolate (5-MTHF) catalyzed by the enzyme methionine synthase (MS), which is dependent on cobalamin (vitamin B12). This process is essential for the regeneration of methionine, a precursor for S-adenosyl methionine (SAM), a universal methyl donor in various biochemical reactions (Figure 3).

The transculturation pathway converts homocysteine to cysteine by enzymatic processes driven by CBS and γ-cystathionase. Homocysteine and serine are converted to cystathionine by CβS, with vitamin B6 acting as a cofactor in both processes. The transculturation pathway's final product, cysteine, can also aid in the synthesis of hydrogen sulfide (H2S), a signaling molecule with a variety of physiological uses. The equilibrium of sulfur-containing amino acids and methyl group availability in the body depends on the strict control of homocysteine metabolism via these routes (Figure 3) (Bhargava, 2018; Li et al., 2021; Herrmann et al., 2022; Khelfi, 2023).

Dysregulation of homocysteine metabolism can lead to hyperhomocysteinemia, a condition associated with various health issues, including cardiovascular diseases and IBD diseases.

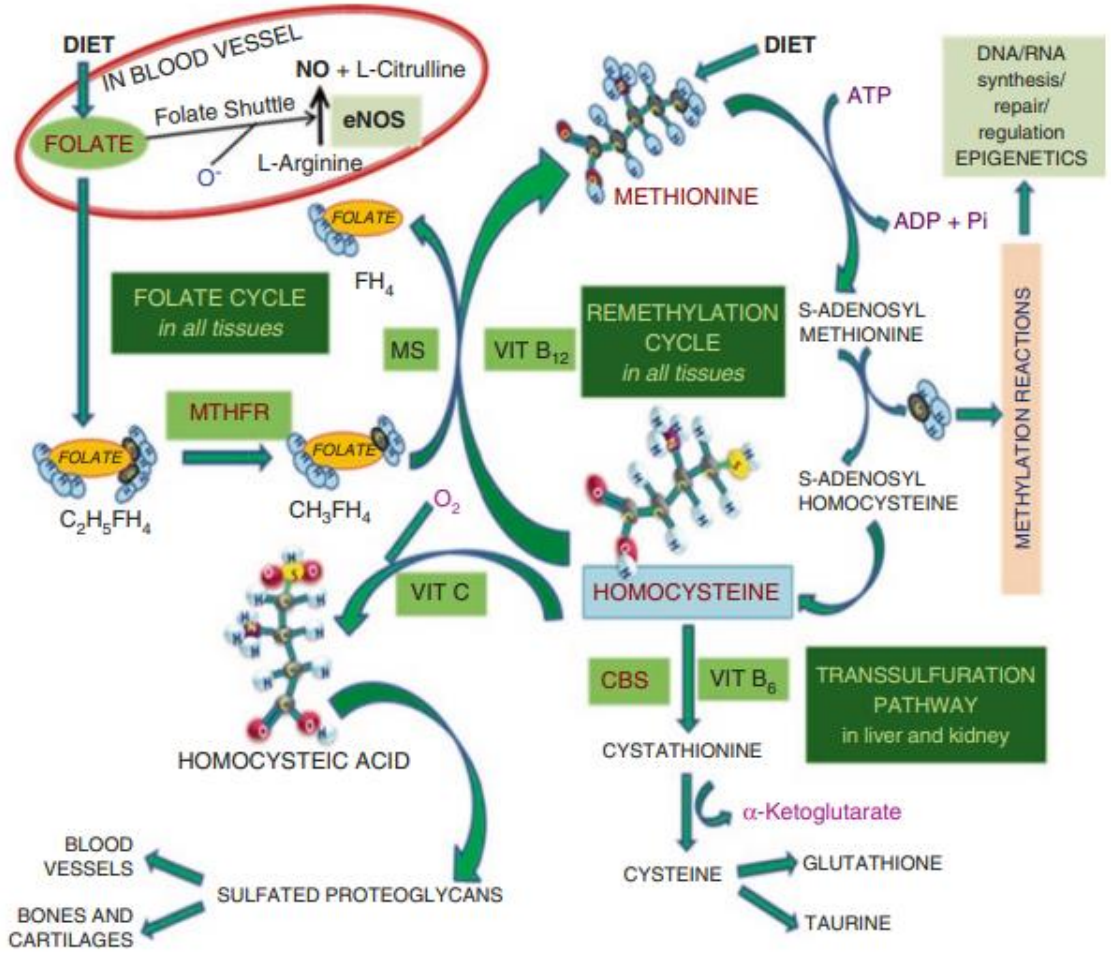

Figure 3. Biosynthesis and metabolism of homocysteine. The metabolism of homocysteine and its association with folate cycle, remethylation cycle and the transsulphuration pathway. NO Nitric oxide, eNOS endothelial nitric oxide synthase, C2H5FH4 methylene tetrahydrofolate, CH3FH4 methyl tetrahydrofolate, FH4 tetrahydrofolate, MS methionine synthase, O2 oxygen, MTHFR methylene tetrahydrofolate reductase, CBS cystathionine beta synthase (Bhargava and Srivastava, 2014).

I.3. Hyperhomocysteinemia and inflammatory bowel disease

Homocysteine level in patients with inflammatory bowel disease is mostly normal or slightly elevated. Disease activity does not have an impact on homocysteine level. Folic acid is the most important factor having an influence on homocysteine level in patients with inflammatory bowel disease (Owczarek et al., 2014). Vitamin B12 and folate deficiency and therapy with antifolate drugs may predispose patients with inflammatory bowel disease (IBD) to hyperhomocysteinemia (Romagnuolo et al., 2001).

I.4. Hydrogen sulfide and inflammatory bowel disease

Hydrogen sulfide (H_2S), originally known as toxic gas, has now attracted attention as one of the gas transmitters involved in many reactions in the human body (Stummer et al., 2023).

Hydrogen sulfide (H2S) plays a complex role in the pathogenesis of inflammatory bowel disease (IBD), exhibiting both pro-inflammatory and anti-inflammatory effects depending on various factors like the disease stage, concentration and cellular localization (kimura, 2011; and Stummer et al., 2023).

Changes in H2S levels, influenced by microbiota, endogenous metabolism, and diet are linked to IBD inflammation. Increased H2S production by sulfate-reducing bacteria (SRB) is associated with active disease and symptom severity in IBD patients, particularly those with ulcerative colitis (UC). Consequently, pharmacological modulation of H2S production and metabolism presents a potential therapeutic approach for treating IBD (Stummer et al., 2023) (Figure 4).

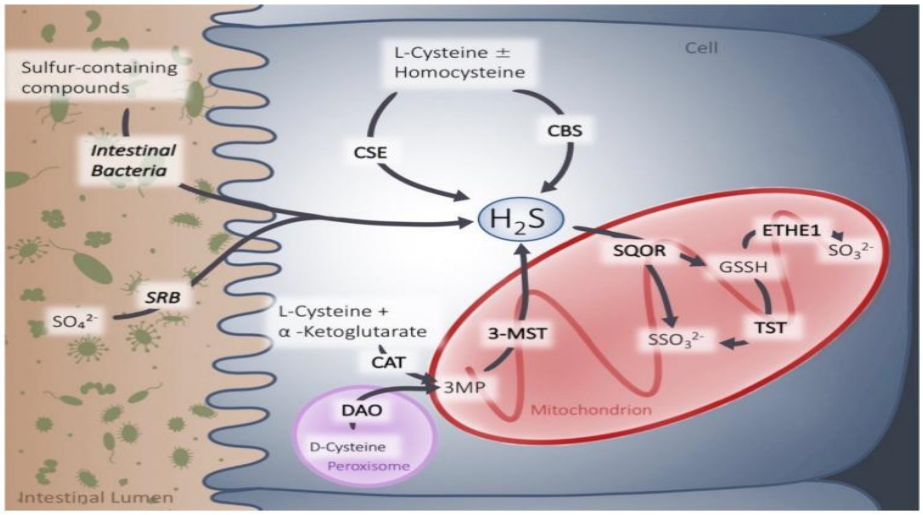

Figure 4. Hydrogen sulfide (H2S) production and detoxification (Stummer et al., 2023).

Exogenous H2S is a metabolic product of the degradation of sulfate (SO42−) through sulfate-reducing bacteria (SRB) or degradation of sulfur-containing compounds by intestinal bacteria. Endogenous H2S results from degradation of L-cysteine with or without homocysteine by cystathionine-γ-lyase (CSE) and cystathionine-β-synthase (CBS) in the cytosol and from 3-mercaptopyruvate (3MP) by 3-mercapto-sulfurtransferase (3-MST) in mitochondria. The detoxification process is catalyzed by sulfide: quinone oxidoreductase (SQOR) and subsequently by thiosulfate sulfur transferase (TST) or ethylmalonic encephalopathy 1 protein (ETHE1). Detoxification occurs solely in the mitochondria. Cysteine aminotransferase (CAT), D-amino acid oxidase (DAO), glutathione persulfide (GSSH), thiosulfate (SSO32−), sulfite (SO32−) (Stummer et al., 2023).

CHAPTER II

Inflammation

II. Inflammation

II.1. Definition of inflammation

Inflammation more broadly as a protective response, involving the activation of immune and non-immune cells, in response to an insult such as infection, toxic compounds, damaged cells, or irradiation, with the aim to restore tissue homeostasis. This raises the question as to whether inflammation is always protective (Bryan et al., 2022).

II.2. Type of inflammation

2.1. Acute Inflammation

Tissue damage due to trauma, microbial invasion, or noxious compounds can induce acute inflammation. It starts rapidly, becomes severe in a short time and symptoms may last for a few days for example cellulitis or acute pneumonia (Pahwa, 2018).

2.2. Chronic inflammation

Chronic inflammation describes an ongoing, long-term response to endogenous or exogenous inflammatory stimuli and is characterized by continued accumulation of mononuclear leukocytes (macrophages and lymphocytes), accompanied by tissue injury due to the prolonged inflammatory response (McManus et al., 2014).

II.3. Mechanisms of the inflammatory response

The inflammatory response is a crucial part of our body's defense system, triggered in response to damage, infection, or foreign material. Let's delve into the mechanisms that orchestrate this intricate process:

3.1. Cellular activation and recruitment

Leukocytes, including neutrophils and monocytes (which later become macrophages), migrate to the site of tissue damage. Granulocytes, such as neutrophils, release histamines, promoting vasodilation around the affected area. Increased blood flow brings immune cells and chemicals to combat infection (Alus, 2024).

3.1.Vasodilation and increased permeability

Vasodilation is a normal response that occurs during inflammatory processes to increase blood flow to affected areas. However, in response to overwhelming infection, our bodies release numerous vasodilatory chemicals **(**histamine) that cause inflammation and can lead to lethal hypotension (Jentzer et al., 2018).

3.3. Neutrophil infiltration

These processes are activated and amplified by a series of intracellular and extracellular factors that tightly co-ordinate the inflammatory process. The innate immune system responds rapidly to infection or injury. Macrophages, natural killer cells, CD8+ T-lymphocytes and neutrophils provide an early response to injurious factors in an effort to contain and eliminate harmful stimuli. The adaptive immune response requires prior exposure to microbial antigens, is mediated primarily by CD4+ T-lymphocytes and serves to further amplify acute inflammation. Although acute inflammation is fundamentally beneficial, severe inflammation can precipitate the systemic inflammatory response syndrome (Edward, 2003).

CHAPTER III

C-reactive protein

III. C-reactive protein

III.1. Definition of C-reactive protein

C-reactive protein is predominantly synthesized in the liver, typically within the transcriptional phase of the response to proinflammatory cytokines. IL-6 appears to be the main regulator, by promoting *de novo* synthesis of CRP via upregulation of C/EBPβ and C/EBPδ, key transcription factors in this process. In addition, IL-6 signaling may be reinforced by IL-1β and TNF, both of which increase transcription rate of CRP. Serum CRP levels have also been closely linked to signaling by proinflammatory cytokines released by visceral adipose tissue (Juan et al., 2014).

III.2. Structure of C-reactive protein

C-reactive protein consists of five identical, noncovalently associated ~23-kDa protomers arranged symmetrically around a central pore. The term "pentraxins" has been used to describe the family of related proteins with this structure. Each protomer has been found by x-ray crystallography to be folded into two antiparallel β sheets with a flattened jellyroll topology similar to that of lectins such as concanavalin A (Steven et al., 2004). It is not glycosylated, and its molecular mass is 115,135 Da (Bienvenu, 2016).

It has a recognition face with a phosphocholine binding site consisting of two coordinated calcium ions adjacent to a hydrophobic pocket. The co-crystal structure of CRP with phosphocholine suggests that Phe-66 and Glu-81 are the two key residues mediating the binding of phosphocholine to CRP . Phe-66 provides hydrophobic interactions with the methyl groups of phosphocholine whereas Glu-81 is found on the opposite end of the pocket where it interacts with the positively charged choline nitrogen. The importance of both residues has been confirmed by mutagenesis studies (Steven et al., 2004) (Figure 5).

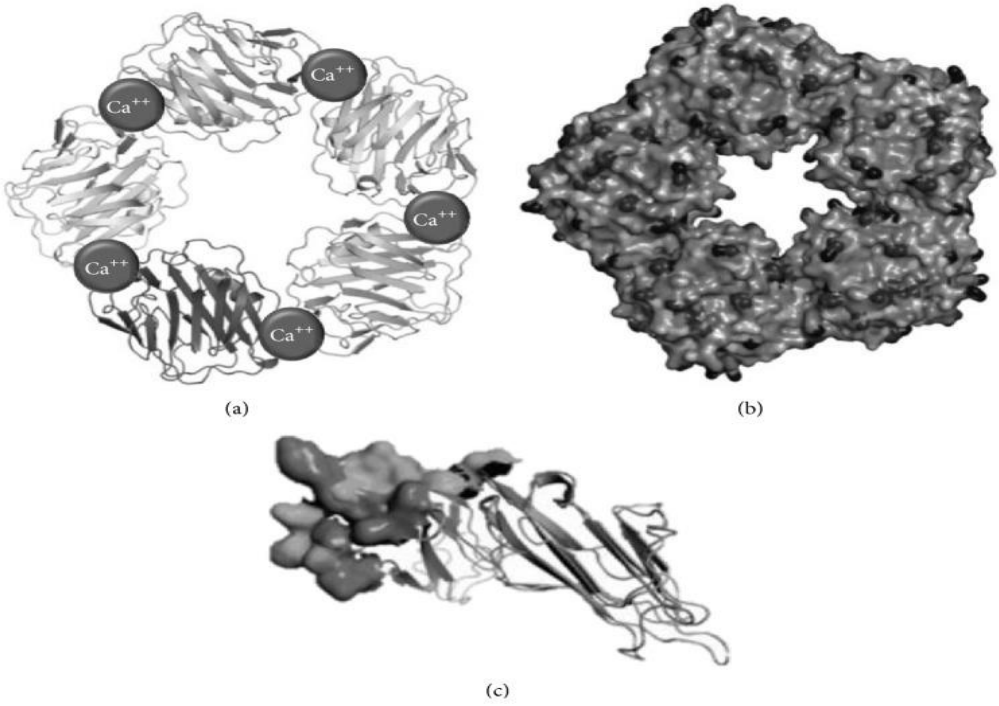

Figure 5. Molecular structure of C-reactive protein (CRP). (a) Tape diagram of CRP, in which the 2 Ca2+ atoms are presented (spheres). These are necessary for ligand binding. (b) Space model of CRP, with a phosphocholine molecule in the ligand binding site. (c) no glycosylated polypeptide subunit of monomeric C-reactive protein (Salazar et al., 2014).

III.3. Function of C-reactive protein

The C-reactive protein has a calcium-dependent affinity for many other ligands. This binding initiates it activation of various host defense systems. Each CRP monomer has a binding site for phosphorylcholine. This is not exposed by the body's cells under normal conditions, and only appears on the altered cell membranes of damaged cells (Bienvenu, 2016).

The main role of CRP in inflammation tends to focus around the activation of the C1q molecule in the complement pathway leading to the opsonization of pathogens, it can also initiate cell-mediated pathways by activating complement as well as to binding to Fc receptors of IgG. CRP binds to Fc receptors with the resulting interaction leading to the release of pro-inflammatory cytokines (Sproston and Ashworth, 2018). CRP is therefore an opsonin for bacterial sequences and nuclear material that is expressed on the cell membrane during apoptosis, it is not only important in the host's innate immune defence but also in the protection against autoimmune diseases by its ability to opsonize and phagocyte nuclear components (Vermeire et al., 2004).

III.4. C-reactive protein and inflammation

C-reactive protein levels are known to increase dramatically in response to injury, infection, and inflammation. It is mainly classified as an acute marker of inflammation. CRP is the principal downstream mediator of the acute-phase response following an inflammatory event (Nicola and Jason, 2018).

High levels of CRP have been associated with various inflammatory conditions such as infections, autoimmune diseases, and cardiovascular diseases. Monitoring CRP levels is essential in diagnosing and managing inflammatory disorders, as it provides valuable insight into disease progression and treatment efficacy (Nicola and Jason, 2018).

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III.5. CRP levels and clinical implications

5.1. Levels

C-reactive protein levels in the blood can provide important information about the presence and intensity of inflammation, and they have various clinical implications:

- Low to moderate elevation (CRP levels 3-10 mg/l). This range can be associated with factors such as obesity, pregnancy, smoking, diabetes, periodontal disease, and mild viral infections like the common cold.
- Moderate elevation (CRP levels over ≥ 10 mg/l). Such levels often indicate more serious inflammatory conditions, including autoimmune disorders like lupus, rheumatoid arthritis, and inflammatory bowel disease.
- High elevation (CRP levels significantly above >10 mg/l). High CRP levels can be a sign of acute bacterial infections, severe chronic inflammation, or other medical conditions such as some cancers (Jennifer and Zawn, 2023).

It's important to note that while CRP levels can indicate the presence of inflammation, they do not pinpoint the exact cause. Therefore, elevated CRP levels typically prompt further investigation and testing to determine the underlying issue (Jennifer and Zawn, 2023).

5.2. Clinical

C-reactive protein (CRP) is a vital biomarker in clinical settings, aiding in the diagnosis and prognosis of inflammatory conditions. Elevated CRP levels are associated with various ailments including cardiovascular diseases, infections, autoimmune disorders, and certain cancers. Monitoring CRP levels helps clinicians assess disease severity, guide treatment decisions, and predict patient outcomes. In cardiovascular health, CRP levels indicate inflammatory activity, aiding in identifying individuals at risk of heart attacks or strokes. Tracking CRP levels also helps evaluate treatment effectiveness, as reductions often correlate with improved clinical outcomes. (Sonawane and Nimse, 2017; Ridker and Cook, 2017; Enabnit, 2023).

CHAPTER IV

Inflammatory bowel disease

IV. Inflammatory bowel disease

IV.1. Definition of inflammatory bowel disease (IBD)

Inflammatory bowel disease is a complex group of disorders involving alterations in gastrointestinal physiology with relapsing-remitting phases.

Those are a chronic immune-mediated inflammatory disease characterized by damage to the epithelial barrier and disruption of immune homeostasis in the gastrointestinal tract and mucosal immunity by a complex inflammatory process (Khelfi, 2023).

IV.2. Anatomy of digestive apparatus

The anatomy of digestive apparatus consists of two parts:

First part

a) **Mouth**. The mouth is equipped with structures like teeth (for chewing), salivary glands (that secrete enzymes for chemical digestion), and the tongue (which detects taste and pushes food toward the pharynx).
b) **Pharynx**. This muscular tube conducts food from the mouth to the esophagus**.**
c) **Esophagus**. A muscular tube that transports the bolus (chewed food) to the stomach**.** It has an upper sphincter (opens during swallowing) and a lower sphincter (controls emptying into the stomach) (Figure 6.a).
d) **Stomach**. The stomach secretes gastric acid (hydrochloric acid + pepsin) that digests proteins and converts the bolus into chime **(**Michael et al., 2011) (Figure 6.a).

The stomach consists of four parts:

1. **The cardia** (where the esophagus empties).

2. Fundus (upper curved part).

3. **Body** (central region).

4. Pylorus (which empties chyme into the duodenum) (Michael et al., 2011) (Figure 6.b).

e) **Small intestine**. The small intestine is a crucial site for nutrient absorption. It consists of three segments:

1. Duodenum. Mixes chyme with bile and secretes bicarbonates to activate pancreatic enzymes.

2. Jejunum. Further absorbs nutrients.

3. Ileum. Completes nutrient absorption (Figure 6.a and Figure 6.b).

f) **Large intestine (Colon)**. The colon absorbs water and electrolytes from the remaining chyme. It includes the cecum**,** ascending colon**,** transverse colon**,** descending colon**,** sigmoid colon**,** and rectum (Michael et al., 2011) (Figure 6.a and Figure 6.b).

Second part

This part consists of accessory organs:

- **Liver**. Detoxifies metabolites, synthesizes proteins, and produces biochemicals needed for digestion.
- **Gallbladder**. Stores bile and releases it into the duodenum.
- **Pancreas**. Secretes insulin, glucagon, and pancreatic juice (containing enzymes for digestion).
- **Spleen**. Breaks down spent red blood cells, leading to the production of bilirubin **(**which is then sent to the liver and secreted in bile) (Michael et al., 2011) (Figure 6.a).

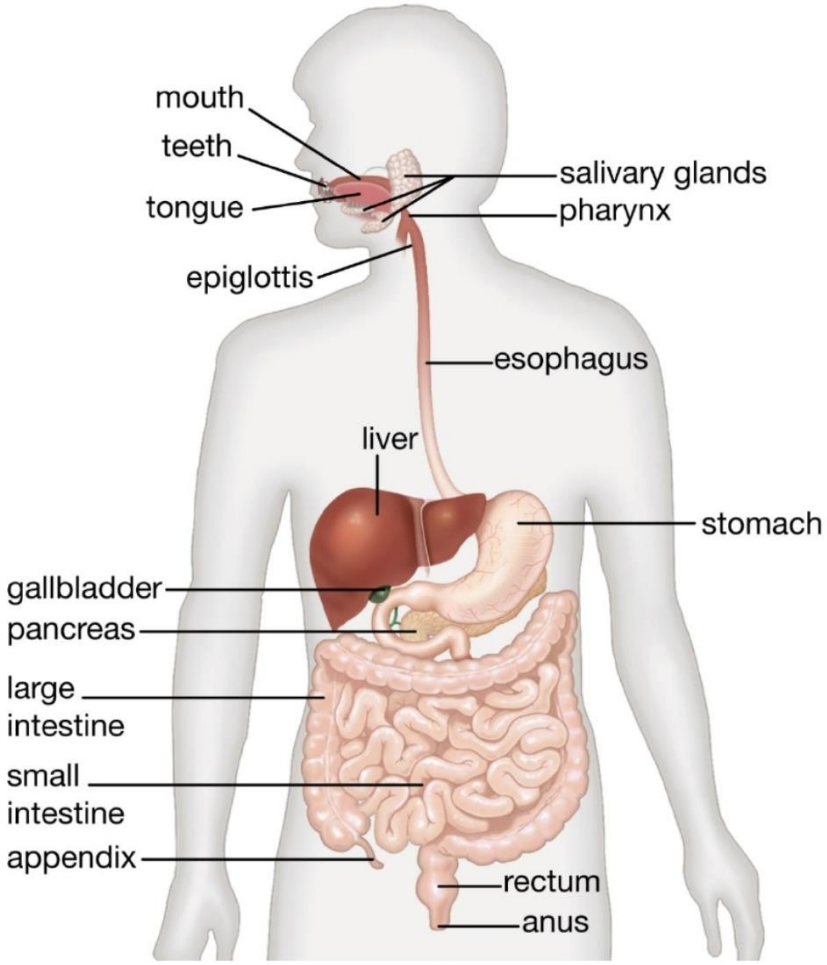


Figure 6.a. Anatomy of human digestive system [1].

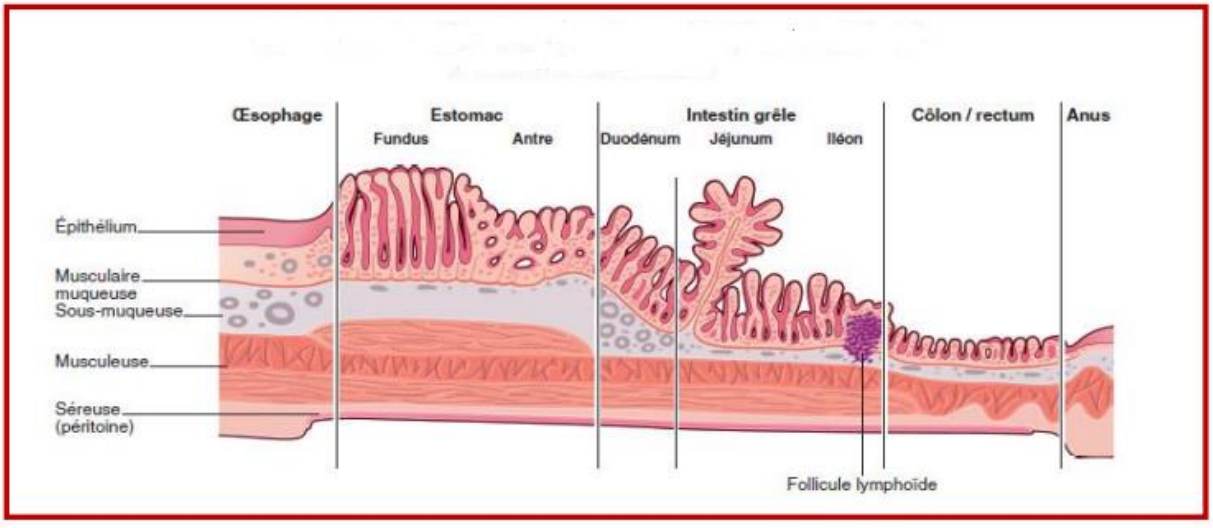


Figure 6.b. Histologic aspect of the digestive wall (Guilherme et al., 2019).

IV.3. Types of inflammatory bowel disease

It encompasses two main types:

3.1. Crohn's Disease (CD)

Crohn's disease (CD) is a condition that results in transmural ulceration of any part of the gastrointestinal tract (GI), most commonly affecting the terminal ileum and colon. The classification of CD is based on its extent (mild, moderate, or severe) and its location (McDowell et al., 2023) (Figure 7.a).

It can be subdivided into inflammatory, structural, or penetrating phenotypes. CD can cause significant morbidity and manifest additional intestinal manifestations beyond the gastrointestinal tract (GI). Unfortunately, it is not curable and increases the risk of colorectal cancer (McDowell et al., 2023) (Figure 7.c).

3.2. Ulcerative colitis

Ulcerative colitis (UC) is a condition that involves diffuse inflammation of the colonic mucosa. The rectum (proctitis) is often affected and can spread to other parts of the colon (Figure 7.a).

The classification of UC is determined by the extent of involvement (such as proctosigmoiditis, distal ulcerative colitis, or pancolitis). As with CD, UC also has extra intestinal manifestations and can cause substantial morbidity. It is not a cure and increases the likelihood of developing colorectal cancer (McDowell et al., 2023) (Figure 7.b).

IV.4. Symptoms of inflammatory bowel disease

Inflammatory bowel disease (IBD), encompassing Crohn's disease (CD) and ulcerative colitis (UC), is marked by chronic inflammation of the gastrointestinal tract and presents with a variety of symptoms. Gastrointestinal manifestations include abdominal pain, cramping, frequent and urgent diarrhea often accompanied by blood, especially in UC, and the presence of mucus in stools. Patients may also experience constipation, sometimes alternating with diarrhea, a feeling of incomplete evacuation after bowel movements, and bloating and gas (Molodecky et al., 2012; Buhner et al., 2020; Cripps, 2021).

Systemic and extraintestinal symptoms frequently reported by patients include fatigue, loss of appetite, weight loss, occasional low-grade fever, joint pain and arthritis, skin conditions like rashes and ulcers, eye inflammation, oral ulcers, and in children, growth retardation and delayed puberty (Peyrin-Biroulet et al., 2010; Lönnfors et al., 2014; Cripps, 2021).

Psychological symptoms such as anxiety, depression, difficulty sleeping, irritability, and mood swings are also common due to the chronic nature and social impacts of the disease (Lönnfors et al., 2014; Cripps, 2021). These symptoms often fluctuate, with periods of remission and flare-ups, highlighting the need for accurate diagnosis through blood tests, stool tests, endoscopic procedures, and imaging studies to assess inflammation and identify complications (Buhner et al., 2020; Cripps, 2021).

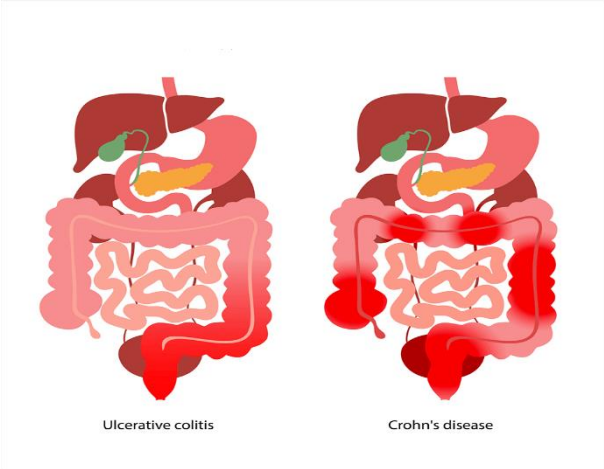


Figure 7.a. Crohn's disease and ulcerative colitis disease [2].

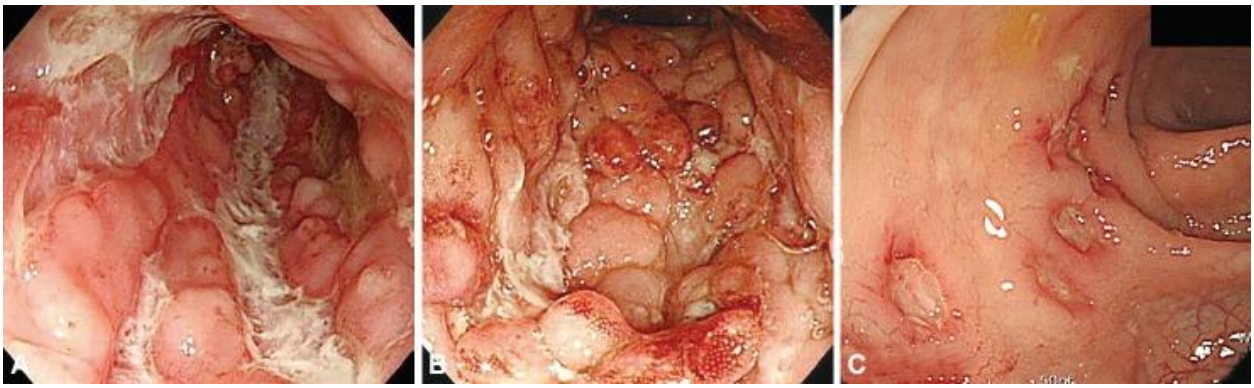


Figure 7.b. Typical endoscopic features of Crohn's disease. (A) Longitudinal ulcers, (B) cobblestone appearance, (C) aphthous ulcers showing longitudinal array (Chang et al., 2016).

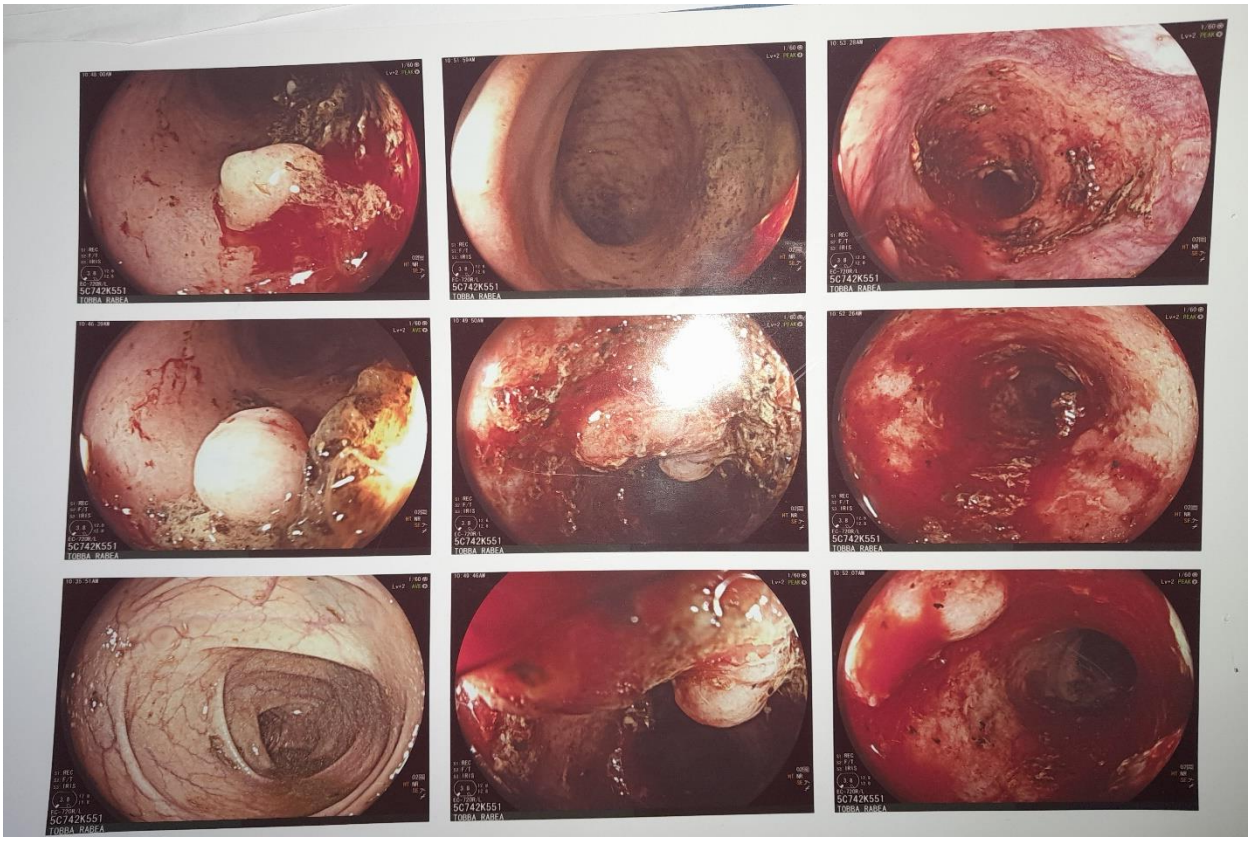


Figure 7.c. Typical endoscopic features of ulcerative colitis of female age 40 years old.

IV.5. Immunopathology in IBD

The intestinal immune system plays a crucial role in the development of inflammatory bowel disease (IBD). Within the intestinal epithelium, intercellular junctions act as barriers, preventing the entry of bacteria and antigens into the circulation. In IBD, these junctions become defective due to either primary barrier dysfunction or severe inflammation. Additionally, protective mechanisms include mucus production by goblet cells and the secretion of α-defensins by the pancreas, which have intrinsic antimicrobial properties. Persistent inflammation leads to ongoing deterioration of the epithelium and increased exposure to intestinal microbes, exacerbating the inflammatory process (McDowell et al., 2023).

Crohn's disease can impact any segment of the gastrointestinal (GI) tract, potentially causing strictures, inflammation, or the formation of fistulas. A defining characteristic of Crohn's disease is its involvement of all layers of the bowel (transmural). In later stages of the disease, the mucosa exhibits a cobblestone appearance due to linear ulcers between areas of normal mucosa (Trivedi and Adams., 2018; Strum et al., 2019; McDowell et al., 2023).

The localized release of specific cytokines, including IL-12, IL-17, TNF-α, and IFN-γ, has been implicated in the chronic intestinal inflammation observed in Crohn's disease patients (Williams, 2012).

Antigen-presenting cells (APCs) and macrophages produce IL-12 and IL-18, leading to polarization toward Th1 lymphocytes, which subsequently release proinflammatory cytokines such as TNF-α and IFN-γ. Additionally, Th1 cytokines stimulate APCs to secrete a broader range of inflammatory cytokines, including IL-1, IL-6, IL-8, IL-12, and IL-18, perpetuating a self-sustaining cycle (Plevy, 2002).

In ulcerative colitis (UC), persistent mucosal inflammation results in edema, ulcers, bleeding, and electrolyte imbalances. The inflammatory process typically initiates in the rectum and then progresses continuously toward the proximal colon (Trivedi and Adams., 2018; Strum et al., 2019; McDowell et al., 2023).

Notably, interleukin-13 (IL-13) plays a significant role in driving inflammation and maintaining the chronicity of UC (Silverberg, 2005). Despite the involvement of Th1 immune responses, UC patients also exhibit a Th2 response characterized by increased secretion of IL-4, IL-5, and IL-9 (Liu et al., 2009; Gerlach et al., 2014).

Researchers have proposed that the transcription factor, the purine –rich box1 (PU.1) is a regulator of cellular communication, along with IL-9 produced by effector Th9 cells, inhibits the proliferation of intestinal epithelial cells and modulates the expression of tight-junction proteins. These factors collectively contribute to the translocation of specific bacterial species, subsequent immune cell activation, and mucosal inflammation in both experimental and human UC (Gerlach et al., 2014). Additionally, similar to Crohn's disease (CD), Th17-related cytokines are elevated in UC (Kobayashi et al., 2008; Monteleone et al., 2012).

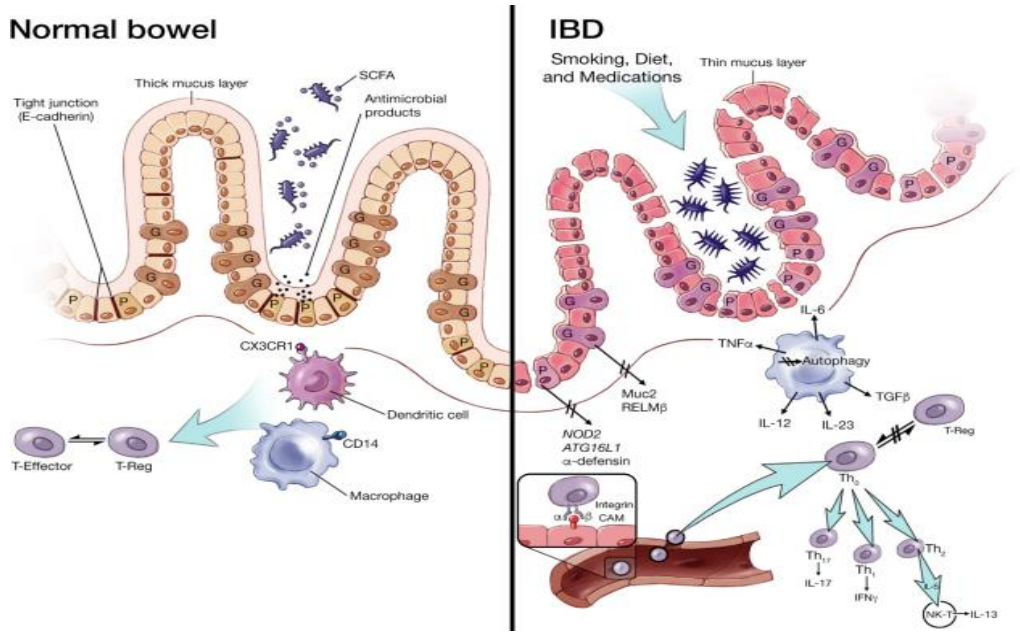


Figure 8. The intestinal mucosa in the normal bowel and in inflammatory bowel disease (IBD) (Ramos and Papadakis, 2019).

On exposure to environmental factors, patients with IBD have development of microbial dysbiosis with a decrease of short chain fatty acids (SCFA) producing bacteria and an increase in proteobacteria. mechanisms that maintain the intestinal barrier are also disrupted in the IBD mucosa, including down-regulation of epithelial cadherin (E-cadherin) in tight junctions; thickness of the mucus layer; abnormal goblet cell function, including mucin 2 (Muc2) and resistin-like molecule b (RELMb) proteins; and dysfunctional Paneth cell associated mechanisms, including secretion of antimicrobial products, nucleotide-binding oligomerization domain containing protein 2 (NOD2), and autophagy-related 16-like 1 (ATG16L1) gene-associated functions. From the innate immune system perspective, the IBD mucosa has been found to exhibit a decrease in colonic macrophages expressing CD14, defective CX3CR1 (C-X3-C motif chemokine receptor 1) antigen presentation by dendritic cells; and impaired autophagy (Ramos and Papadakis, 2019).

Lastly, although leukocyte migration via integrin cellular adhesion molecule (CAM) interactions also occurs in the normal mucosa, the balance between effector and regulatory T cells (T-reg) appears to be disturbed in the IBD mucosa, resulting in uncontrolled activation of different T-cell lineages that migrate to the inflamed intestine (Ramos and Papadakis, 2019).

CHAPTER V

Materials and methods

V. Material and methods

V.1. Materials

This study is carried from March to May, where we have selected tweety two patients diagnostic at the hospital IBEN BADIS (Algeria) with Crohn's disease and compared with control group values.

CRP and hemoglobulin were recorded during questionary and venous blood of seven patient's female (3) and male (4) were collected in sterile vacutainer tubes containing heparin and taken immediately to analysis laboratory (IBSSINA) for the measurement of homocysteine.

V.2. Methods

2.1. Biochemical analysis

Measurement of homocysteine

The plasma values of homocysteine were measured by competitive solid phase chemiluminescence immunoassay on an (IMMULITE). The values of homocysteine were expressed in (µmol/l).

2.2. Histological and morphological investigations

A. Histological study

After the surgery of the patient infected with Crohn's disease a tissue sample is taken from the colon which cut to a small piece and conserved in the formol solution for 24 -48 hours at room temperature. and then it is taken to histologic laboratory to continue the rest of histological steps shown in annex.

B. Morphological study

Two patients from Tebessa hospital infected with Crohn's disease, one female age 21years old and the other male age 24years old who are requested for endoscopic tests where we have taken some photos from there.

2.3. Statistical analysis

The student t statistical analysis was used for the comparison between two groups using logical statist SPSS version 29.

CHAPTER VI

Results and discussion

VI.1. Results

This study population (Group 1) consisted of 22 patients (mean, age18-69). These subjects suffered with Crohn's disease. The main clinical and biological characteristics of patients are given in table (1) and are compared with control values (group 2).

Table 1. Baseline characteristic of the study subjects

Variable	Patients (Group1) Mean ±SEM	Control values (Group2)
Sex M/F	12/10	12/10
Age	33,23 ±11,56 (18-69)	33,23
Homocysteine (µmol/l)	15,54 ±1,29 (21,9-11,3)	12,82 ±0,27
CRP (mg/l)	21,41 ±34,69 (131-3)	<6
Hemoglobin (g/dl)	11,85 ±0,47 (16,1-9)	14,54 ±0,10

1.1. Biochemical results

Homocysteine

The parameter of homocysteine is shown in (Figure 9) and (Table1). Where the concentration of homocysteine in patients was (15,54 µmol/l ±1,29) and control group was (12,82 µmol/l ±0,27). The statistical analysis demonstrated that the concentration of homocysteine is increased but not significantly different from control group 2 P≥ 0,05.

C-reactive protein

The parameter of CRP is shown in (Figure 10) and (Table 1) and the concentration of CRP in patients are increased when compared to the control group with a value of (21,41 mg/l ±34,69)

(≤ 6 mg/l) respectively.

Hemoglobin

The data showed that the hemoglobin concentration is decreased very highly significantly in group1 when compared to the group2. The concentrations were (11,85 g/dl ±0,47) and (14,54 g/dl ±0,10) respectively P<0,001 (Figure 11) and (Table 1).

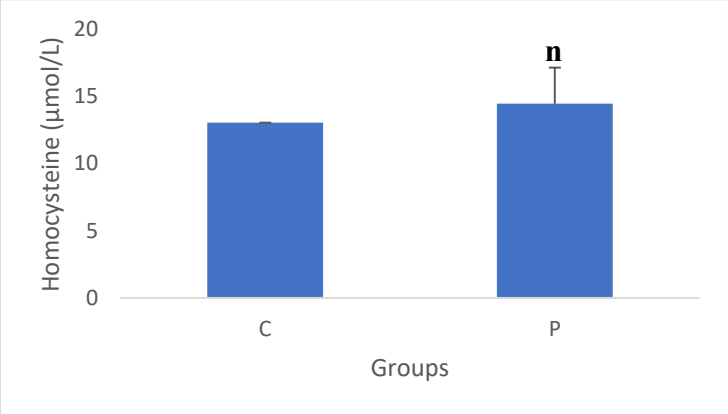


Figure 9. Concentration of homocysteine in human plasma.

P: Patient, C: control P≥0,05 n= not significantly.

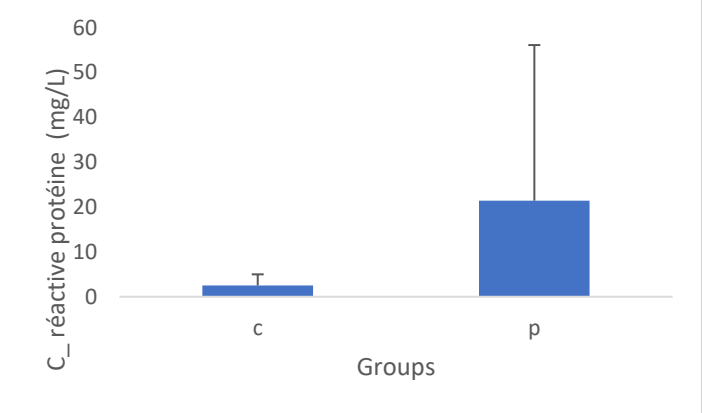


Figure 10. Concentration of CRP in human plasma.

P: Patient, C: control.

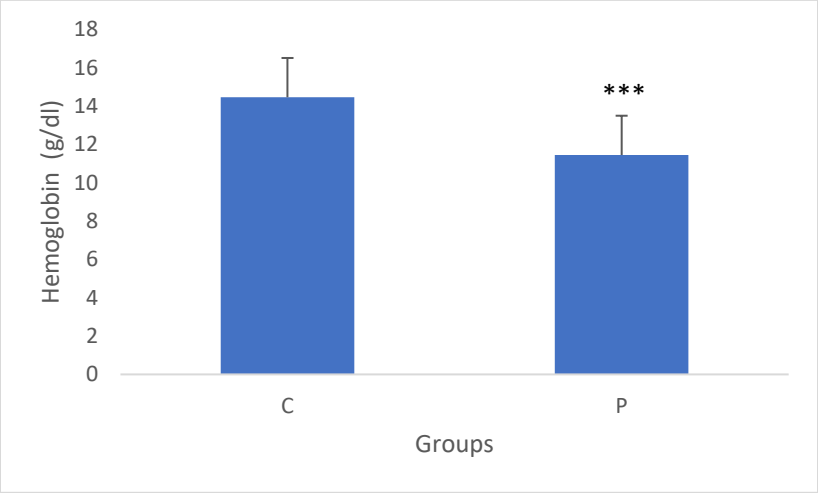


Figure 11. Concentration of hemoglobin in human plasma.

P: Patient, C: control P≤0,001.

1.2. Histological investigations

Histopathological examinations in colon of patient infected with Chron's disease demonstrated an appearance of structural alterations on colon layers, This was observed through crypt degeneration (Figures 12, 14 and 16) muscular lysis (Figure12) and infiltration cellular (Figure 13 and 17).

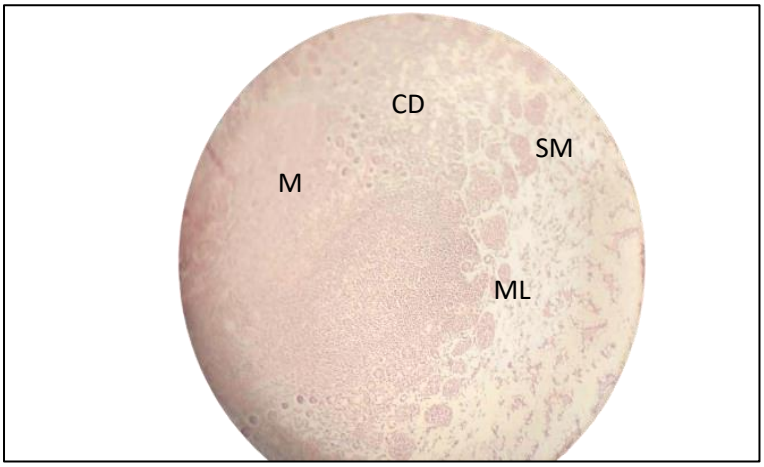


Figure 12. Histological section of colon in patient infected with Crohn's disease.

CD: crypt degeneration. ML: muscular lysis.

M: mucosa. SM: submucosa.

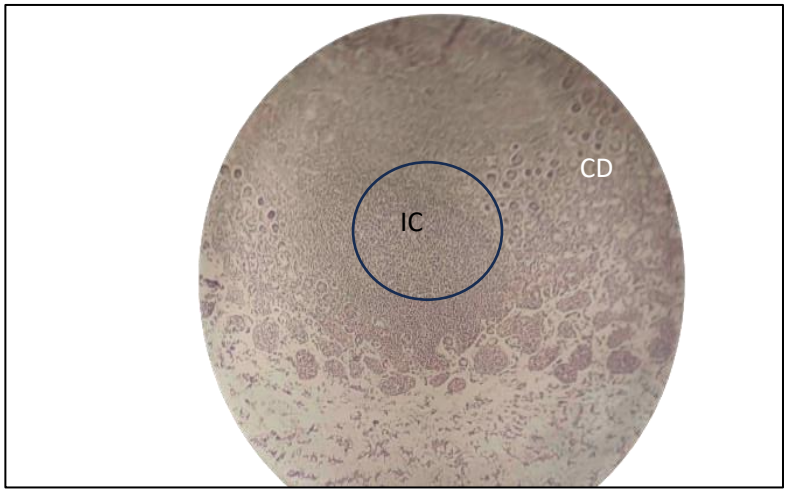


Figure 13. Histological section of colon in patient infected with Crohn's disease.

IC: infiltration cellular, CD: crypt degeneration.

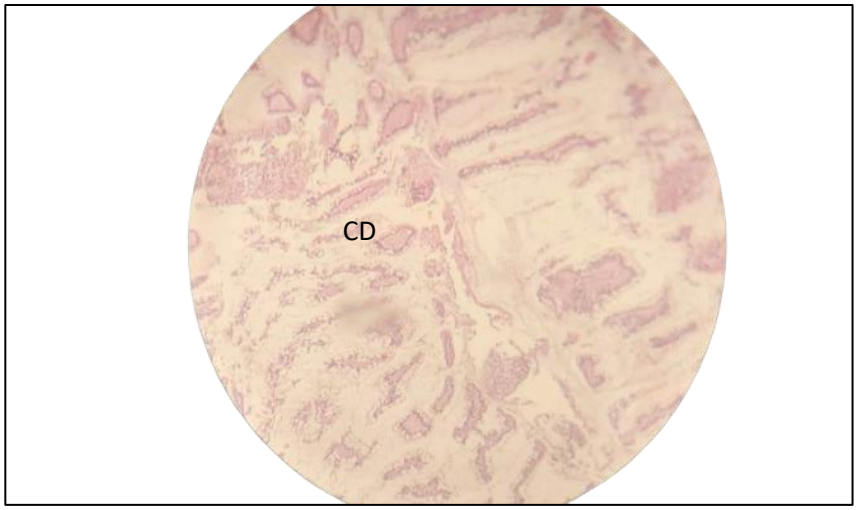


Figure 14. Histological section of colon in patient infected with Crohn's disease.

CD: crypt degeneration.

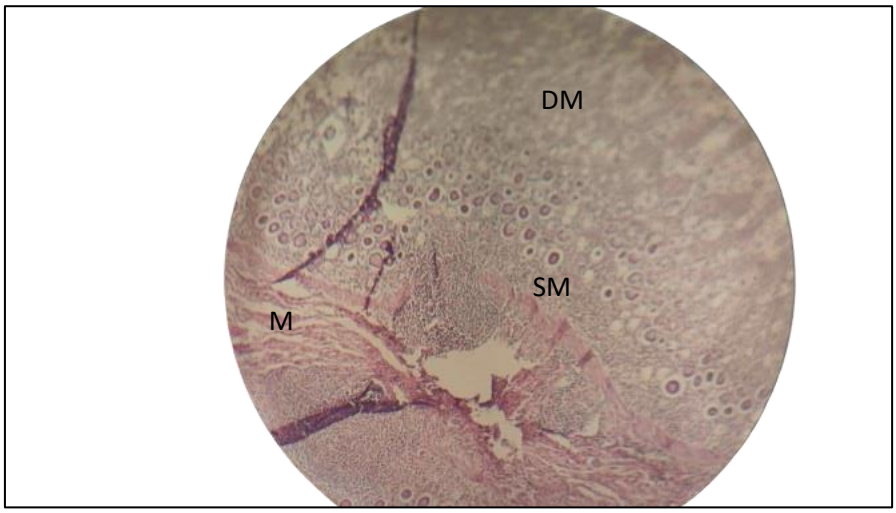


Figure 15. Histological section of colon in patients.

DM: degeneration of the mucosa, SM: sub mucosa, M: Muscularis.

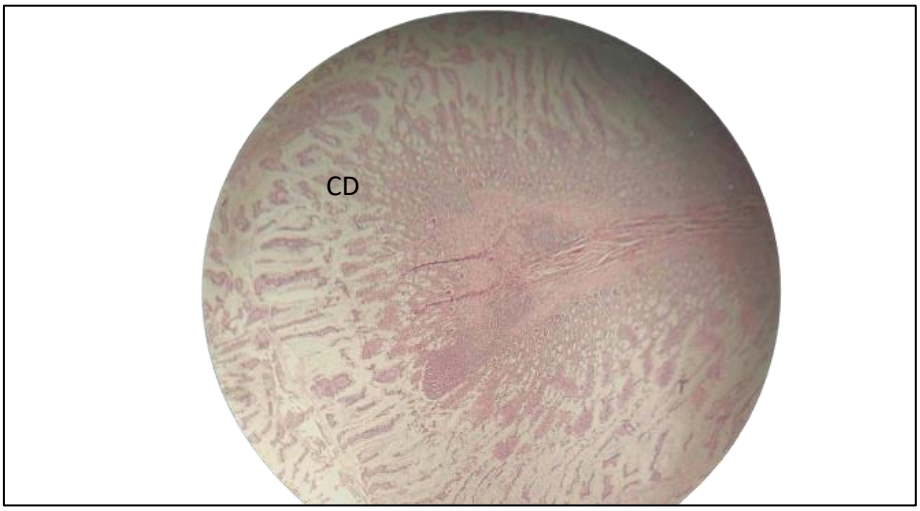


Figure 16. Histological section of colon in patient infected with Crohn's disease.

CD: crypt degeneration.

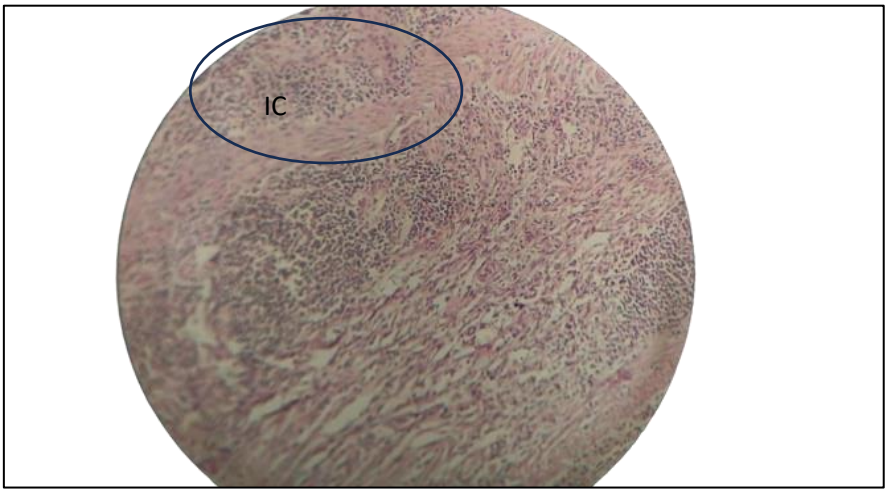


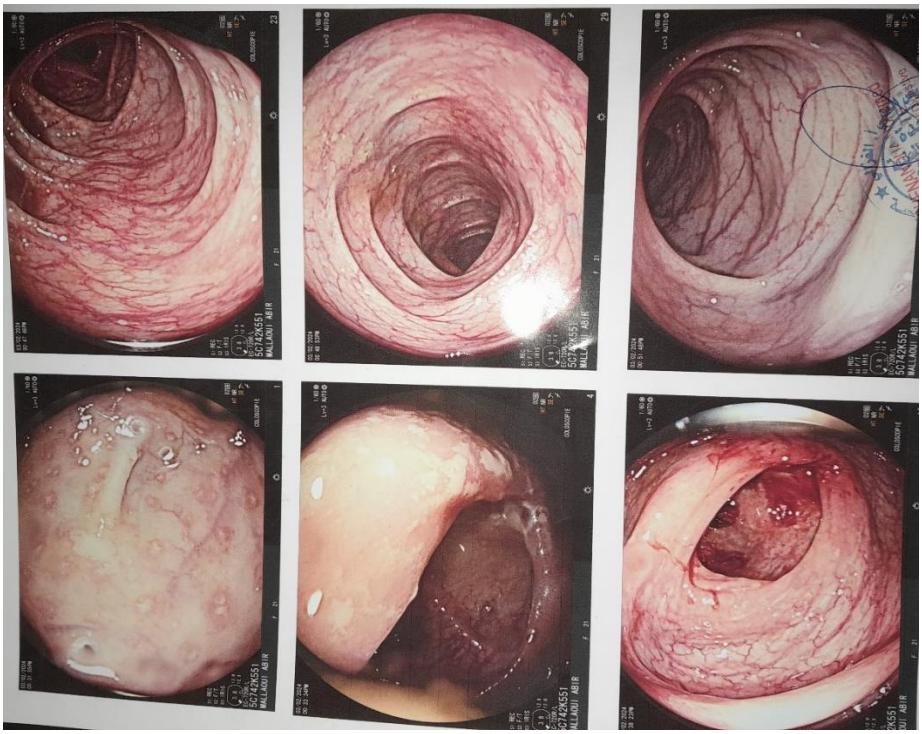
Figure 17. Histological section of colon in patient infected with Crohn's disease.

IC: Infiltration cellular.

1.3. Morphological investigations

The endoscopy analysis demonstrated erosive, inflammatory ileo-cæecal intersection which proved the Crohn's disease in one female patient in Tebessa region (Figure 18).

Ileo-cæecal valve: deformed ulcerated stenotic impassable which proved the Crohn's disease in one male patient in Tebessa region (Figure 19).



Figuer18. Endoscopy of colon infected with Crohn's disease in female age 21 years old.

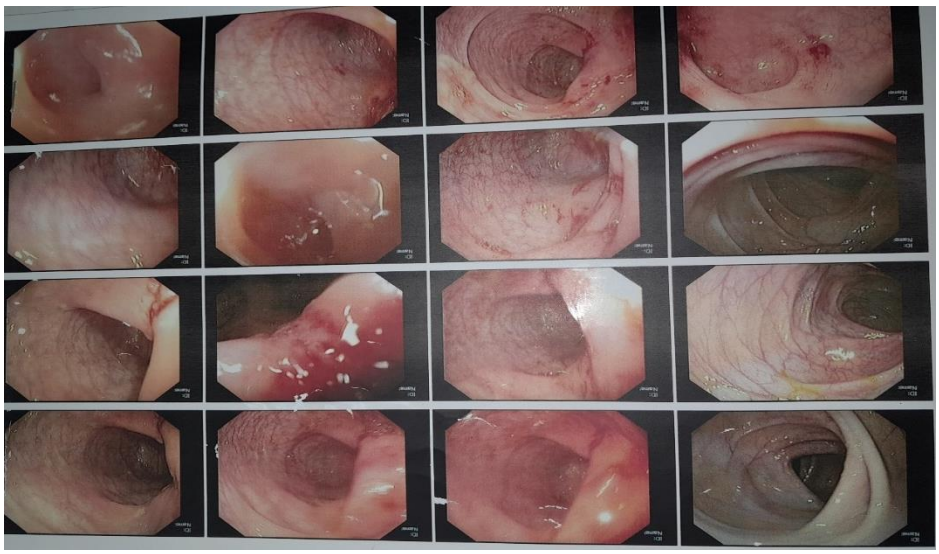


Figure 19. Endoscopy of colon infected with Crohn's disease in male age 24 years old.

VI.2. Discussion

The principal findings in human clinical investigations are the increased levels of amino thiol, homocysteine in patient with Crohn disease as compared with control group, suggesting that this sulfur amino acid, homocysteine is risk factor in Algerian people infected with Crohn disease.

There were increased levels C-reactive protein and low concentration of hemoglobin.

In this clinical study we have observed a moderate level of homocysteine in three patients suffering with Crohn disease. Our results are agree with the work of Zerizer et al. (2008) who obtained during her study in cardiovascular disease moderate hyperhomocysteinemia in group of patients suffering from infactus myocardial where the concentration of homocysteine was between 15,76µmol/l and 23,79 µmol/l.

As mentioned before that moderate hyperhomocysteinemia is an independent risk factor for atherosclerosis (Zerizer et al., 2008).

In seven cases of patients suffering with Crohn disease the concentration of homocysteine was (11,30-21,90 µmol/l).

In this investigation, we obtained in male patients (n=4) and females patients (n=3) that homocysteine showed a sex related differences, where the levels are higher in men than in women 17,23 and 13,2 µmol/l respectively.

The amount of various species of homocysteine in plasma is lower in premenopausal women than in young men. In postmenopausal women the levels approach or even exceed those seen in men (Stabler et al., 1987).

Various studies have suggested that homocysteine levels may be elevated in adults with inflammatory bowel disease (IBD) (Eikelboom et al., 1999; Oldenburg et al., 2000). where increased homocysteine levels put patients at risk for thromboembolic events, such as peripheral venous thrombosis, cerebrovascular stroke syndrome, or manifestations of microvascular injury (Chowers et al., 2000 and Oldenburg et al., 2000).

In our research we have detected that there is a relation between hyperhomocysteinemia and inflammatory bowel disease (IBD), which is in accord with the results of Khelfi. (2023) who

reported that the homocysteine was increased in group of mice treated with L-methionine (200/kg) during 21days and observed alterations in the structure of intestinal mucosa.

Khelfi. (2023) reported that hyperhomocysteinemia is considered to be one of the risk factors for inflammatory bowel disease (IBD) and it is a chronic, relapsing, and remittent inflammatory disease of the gastrointestinal tract.

Maire et al. (2001) reported that more than half of the patients with Crohn's disease have hyperhomocysteinemia. Erzin et al. (2008) reported that IBD patients have a higher prevalence of hyperhomocysteinemia have a higher level of homocysteine than to healthy control.

In our results we found that, the concentration of C-reactive protein (CRP) in patient is increased when we compared to the control group. Henriksen and his group in 2008, reported that **C**-reactive protein (CRP) levels are often used in the follow-up of patients with inflammatory bowel disease (IBD).

A study conducted by Langhorst et al. (2008), who found that IBD patients with active inflammation have high CRP levels. Also, by Vermeire et al. (2004) demonstrated that CRP a valuable marker to detect and follow up disease activity in Crohn’s disease (CD).

Patients with Crohn's disease had a stronger CRP response than did those with ulcerative colitis. In patients with ulcerative colitis, CRP levels at diagnosis increased with increasing extent of disease (Henriksen et al., 2008).

Clinical symptoms of CD and an elevated CRP level are consistent with disease recurrence (Lewis, 2001). However, also levels of CRP occur in non-IBD enteritis, inflammatory disorders not related to the gastrointestinal tract, tissue damage, diabetes, malignancies, and cardiovascular disease (Bohula et al., 2015; Sharma et al., 2018). The sensitivity of CRP measurement is also limited with respect to IBD however normal CRP levels can be seen in patients with active IBD (Fagan et al., 1982).

Peng et al. (2020) reported that CRP levels may also be normal in asymptomatic patients with mild mucosal lesions, especially isolated involvement of the ileum.

Suk et al. (2006) found that the level of CRP differed among individuals with the same inflammatory conditions owing to genetic factors. Age, sex, and body mass index also affect the

serum levels of CRP. Although CRP levels correlate well with CD and patients present with higher levels than those with UC.

In this clinical study we have observed a level of CRP reached to 131 mg/l in one patient suffering with Crohn disease who programed for surgery. Our result is agree with the work of Henriksen et al. (2008) who reported in his study that CRP is a predictive factor for intestinal resection in patients with Crohn's disease and a significant association between intestinal resection during follow-up and CRP levels at diagnosis was only observed for Crohn's disease involving terminal ileum (L1). The risk of surgery increased when CRP at diagnosis was above 53 mg/l, and elevated CRP levels in patients with Crohn's disease at 1 year increased the risk of surgery during the subsequent 4 years.

In our research results we have detected a low concentration of hemoglobin in patients with IBD which agree with Straub et al. (2015), he stated that anemia is a common extraintestinal manifestation of inflammatory bowel disease (IBD) and is frequently overlooked as a complication. Patients with IBD are commonly found to have iron deficiency anemia (IDA) secondary to chronic blood loss, and impaired iron absorption due to tissue inflammation. Patients with iron deficiency may not always manifest with signs and symptoms; so, hemoglobin levels in patients with IBD must be regularly monitored for earlier detection of anemia.

Mahadea et al. (2021), reported that inflammatory bowel disease (IBD) which includes Crohn's disease, is characterized by chronic inflammation of the gastrointestinal tract. IBD has been associated with numerous symptoms and complications, with the most common being iron deficiency anemia (IDA). Iron deficiency in IBD is caused by inadequate intake, malabsorption (including duodenal involvement and surgical removal), and chronic blood loss by mucosal ulcerations.

Evstatiev et al. (2011), reported that anemia is considered the most common metabolic complication of inflammatory bowel disease.

Also, our results agree with Dagmara et al. (2021), who found in his study that the anemia is a common extraintestinal manifestation of inflammatory bowel disease (IBD) and is frequently

overlooked as a complication. Patients with IBD are commonly found to have iron deficiency inflammation. Patients with iron deficiency may not always manifest with signs and symptoms.

Another research reaffirmed that anemia, which is considered the most common metabolic complication of inflammatory bowel disease, has been associated with an impairment in quality of life and cognitive function (Akhuemonkhan et al., 2010).

We have detected in our clinical study levels of hemoglobin reached to 9,6 g/dl in man and 8,3 g/dl in woman which agree with the concentration proposed by the World Health Organization (WHO), where, it can be defined anemia as hemoglobin level <13 g/dl in men or <12 g/dl in non-pregnant women (Akhuemonkhan et al., 2010; Dignass et al., 2015; Koutroubakis et al., 2016).

The European Crohn's and Colitis Organization (ECCO) guidelines classify anemia in IBD patients as iron deficiency anemia (IDA), anemia of chronic disease (ACD), and B12 or folic acid deficiency-associated anemia. (Akhuemonkhan et al., 2010; Foteinogiannopoulou et al., 2021).

Sindhu et al. (2015) describe that anemia in IBD patients involves multiple pathogenic mechanisms resulting in low hemoglobin levels and compromised quality of life. Although ongoing blood loss from chronically inflamed intestinal mucosa and micronutrient deficiency (iron and B12) are the main mechanisms underlying the development of anemia in patients with IBD, chronic inflammation, hemolysis, and medication-induced myelosuppression may also play important roles in both the development of anemia and the management of this condition. This result agrees with our results where we found that hemoglobin is decreased in patient infected with Crohn's disease.

Sindhu et al. (2015) also reported that anemia in IBD is mostly multifactorial, resulting, on the one hand, from chronic intestinal blood loss from inflamed intestinal mucosa combined with impaired iron absorption mainly as a consequence of inflammation.

Conclusion

Conclusion

This research work focuses on the epidemiological investigation, hyperhomocysteinemia, anemia on the Crohn's disease of Algerian people. Homocysteine, CRP and hemoglobin are the biomarker of this study.

Our results confirmed that the high levels of homocysteine and CRP both are imported for the detection of Crohn's disease and a decrease in hemoglobin.

Otherwise, the histological analysis of patient colon shows alterations and destructions in the tissue layers. And the morphological investigations demonstrated, erosive, inflammatory ileo-cæcal intersection and ulcerated stenotic.

For this reason, we recommended to analysis beside CRP and the hemoglobin, the sulfur amino acid homocysteine to reduce the risk of this diseases.

For future work we need to:

Use more number of patients.

Measurement of vitaminsB6, B9 and B12.

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Summary

Summary

Inflammation of the intestine, is a complex process, including two major diseases: Crohn's disease and ulcerative colitis, grouped as inflammatory bowel disease (IBD) which characterized by chronic inflammation in the bowel wall, it can lead to a wide range of symptoms, including abdominal pain, diarrhea, rectal bleeding, and impaired quality of life.

This study was carried in symptomatic patients with Crohn's disease (n=22) at IBEN BADIS Hospital in Algeria and compared to a control group. Homocysteine, CRP and hemoglobin levels were measured. In the histological study we have detected destruction and degeneration in the glands in mucosa layer and also lysis in smooth muscular layer. on the other hand, the endoscopy analysis demonstrated erosive, inflammatory ileo- cæcal intersection and deformed ulcerated stenotic impassable which proved Crohn's disease in one patient female and one patient male.

The results showed that homocysteine (15,54 ±1,29 µmol/l) is increased in patients but not significantly when compared to the control group, the C-reactive protein (21,41 ±34,69 mg/l) is increased also in patients and the concentration of hemoglobin (11,85 ±0,47 g/dl) is decreased very highly significantly. In this study we have detected a moderate level of homocysteine (21,9 µmol/l).

The main value of homocysteine (17,23 µmol/l) in men was increased when compared to women (13,2 µmol/l).

We concluded, that homocysteine is a risk factor for Crohn's disease in Algeria people.

Key words: IBD, hyperhomocysteinemia, CRP, Crohn's disease, anemia, hemoglobin.

Résumé

L'inflammation intestinale, un processus complexe, comprenant deux maladies majeures : la maladie de Crohn et la rectocolite hémorragique, regroupées sous le terme de maladies inflammatoires de l'intestin.

Laquelle caractérisées par une inflammation chronique de la paroi intestinale qui peuvent entraîner une gamme variée de symptômes, notamment des douleurs abdominales, des diarrhées, des saignements rectaux et une altération de la qualité de vie.

Cette étude a été réalisée chez des patients symptomatiques atteints de la maladie de Crohn (n=22) de l'hôpital IBEN BADIS en Algérie et comparée à un groupe témoin . Les taux d'homocystéine, de CRP et d'hémoglobine ont été mesurés.

Dans la partie histologique on a observé des altérations et dégénérescence dans les glandes situées dans la muqueuse et une lyse dans les cellules musculaire lisse. D'autre part l'analyse endoscopique a mis en évidence une ulcération iléo-caecale érosive et inflammatoire et une sténose ulcérée déformée infranchissable qui prouve la maladie de Crohn chez une femme et un homme respectivement.

Les résultats ont montré que l'homocystéine (15,54 ±1,29 µmol/l) est augmentée chez les patients mais pas de manière significative par rapport au groupe témoin, la protéine C-réactive

(21,41 ±34,69 mg/l) est également augmentée chez les patients et la concentration d'hémoglobine (11,85 ±0,47 g/dl) est diminué de manière très significative. Dans cette étude, nous avons détecté un taux modéré d'homocystéine (21,9 µmol/l).

La valeur principale de l'homocystéine (17,23 µmol/l) chez les hommes a été augmentée par rapport aux femmes (13,2 µmol/l).

En conclusion, Cette étude a révélé que l'homocystéine est un facteur de risque de la maladie de Crohn chez les Algériens.

Mots clés : MICI, hyperhomocystéinémie, maladie de crohn , CRP ,anémie , hémoglobine .

ملخص

يعتبر التهاب الأمعاء، عملية معقدة، تشمل مرضين رئيسيين: مرض كرون والتهاب القولون التقرحي، والذي يتميز بالتهاب مزمن في جدار الأمعاء، ويمكن أن يؤدي إلى مجموعة كبيرة من الأعراض، بما في ذلك آلام في البطن، الإسهال، نزيف المستقيم.

جريت هذه الدراسة على مرضى يعانون من اعراض مرض كرون يقدر ب22 مريض بمستشفى ابن باديس في الجزائر والتي تمت مقارنتها مع مجموعة قيم الطبيعية لأشخاص غير مرضى لقد تم قياس خلال هذه الدراسة كل من الهيموجلوبين البروتين النشط س CRPومستويات الهوموسستيين اما في الدراسة النسيجيةلاحظنا تحليل في الغدد المعوية المتواجدة في الطبقة المخاطية مع تحليل في الخلايا العضلية الملساء

ومن خلال الدراسة المورفولوجية عن طريق التنظير لاحظنا تأكل والتهاب التقاطع اللفائفي الاعوري وتشوه متقرح تضيقي غير سالك التي اثبتت مرض كرون في الاناث والذكور على التوالي.

اظهرت النتائج ارتفاع مستوى الهوموسستيين (1,29± 15,54ميكرو مول/لتر) لدى المرضى ولكن ليس بشكل معتبر عند مقارنته بمجموعة الشاهد، كما ارتفع بروتين سي التفاعلي (34,69± 21,41 مليغرام/لتر) لدى المرضى اما تركيز الهيموجلوبين (0,47± 11,85 غرام/ديسيلتر) انخفض بقيمة جد معتبرة. في هذه الدراسة تحصلنا على مستوى معتدل من الهوموسستيين والمقدر ب (21,9ميكرو مول/لتر).

ارتفعت القيمة الرئيسية الهوموسستيين والمقدرة ب (17,23 ميكرومول/لتر) لدى الرجال مقارنة بالنساء التي كانت قد وصلت الى (13,2 ميكرومول/لتر).

في الخاتمة ان النتائج المتحصل عليها تبين أن الهوموسستيين هو عامل خطر للإصابة بمرض كرون في الجزائر.

الكلمات المفتاحية: مرض التهاب الأمعاء، فرط الهوموسستيين،CRP ، فقر الدم، مرض كرون.

ANNEXE

Preparation of histological sections

1. **Fixation**
2. **The samples were taken from the formol solution**
3. **Dehydration**

Dehydration was performed through a series of ethanol solution baths:

- First bath: 60% ethanol (3 x 15 minutes)
- Second bath: 80% ethanol (3 x 15 minutes)
- Third bath: 95% ethanol (3 x 15 minutes).

they were cleared in xylene for 10 min with two exchanges.

4**. Insertion into paraffin**

In this step, the samples were immersed in paraffin at 60°C for 24 hours. Then the cut was made with a thickness of 5 μm using a microtome.

5. Coloring stage

The samples were placed in two xylene baths for 15 minutes each. After this time, they were placed in ethanol baths with decreasing concentrations:

- First bath: 95% ethanol 5 min
- Second bath: 80% ethanol 5 min
- Third bath: 60% ethanol for 5 min.

The samples were placed in hematoxylin for 5-10 minutes, and then washed with tap water. After that the sample colored with eosin for 2-4 minutes, after this time they were washed with tape water.

Samples dried on the heating plate at 37°C. After this stage, the samples are ready for viewing under a microscope.

Année universitaire : 2023-2024	**Présenté par :** KHELLAFI Hiba Rahma FARHI Sarra

Hyperhomocysteinemia and Crohn's disease in Algeria people

Mémoire pour l'obtention du diplôme de Master II

Inflammation of the intestine, is a complex process, including two major diseases: Crohn's disease and ulcerative colitis, grouped as inflammatory bowel disease (IBD) which characterized by chronic inflammation in the bowel wall, It can lead to a wide range of symptoms, including abdominal pain, diarrhea, rectal bleeding, and impaired quality of life.

This study was carried in symptomatic patients with Crohn's disease (n=22) at IBAN BADIS Hospital in Algeria and compared to a control group. Homocysteine, CRP and hemoglobin levels were measured. In the histological study we have detected destruction and degeneration in the glands in mucosa layer and also lysis in smooth muscular layer. on the other hand, the endoscopy analysis demonstrated erosive, inflammatory ileo- cæcal intersection and deformed ulcerated stenotic impassable which proved Crohn's disease in one patient female and one patient male respectively.

The results showed that homocysteine (15,54 ±1,29 µmol/l) is increased in patients but not significantly when compared to the control group, the C-reactive protein (21,41 ±34,69 mg/l) is increased also in patients and the concentration of hemoglobin (11,85 ±0,47 g/dl)is decreased very highly significantly . In this study we have detected a moderate level of homocysteine (21,9 µmol/l). The main value of homocysteine (17,23 µmol/l) in men was increased when compared to women (13,2 µmol/l).

We concluded, that homocysteine is a risk factor for Crohn's disease in Algeria people.

Mots clés: IBD, hyperhomocysteinemia, CRP, Crohn's disease, anemia, hemoglobin

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