**Table S1.** Main mediators of the cardiorenal, nervous, and endocrine systems.

| Regulation of body fluids under physiological conditions | | | | | |
|---|---|---|---|---|---|
| **Cardiac** | | **Renal** | | **Endothelial** | |
| **Preload – contractility – postload**. | | **Regulate osmolality, electrolyte balance and acid-base balance** | | **Control of vascular tone** | |
| **Mediator** | **Actions** | **Mediator** | **Actions** | **Mediator** | **Actions** |
| **Atrial Natriuretic Peptide (ANP)** | ↓ Regulates intravascular volume through the relaxing effect it produces on vascular smooth muscle cells;<br>↓ Blood pressure by reducing sympathetic tone and inhibiting endothelin-1 (ET-1)/secretion and decreases sodium retention;<br>↑ Antagonist of RAAS. | **Prostaglandins (PGE2 and PGD2)** | ↑ Vasodilation | **Nitric Oxide (NO)** | ↑ Relaxation of arterial and venous vasculature |
| | | **Thromboxane A (TXA)** | ↑ Vasoconstriction | **Prostacyclins** | ↑ Vasodilation |
| | | **Atrial Natriuretic Factor (ATF)** | ↑ Excretion of sodium and water by the kidneys | **Thromboxane A (TXA)** | ↑ Vasoconstriction |
| | | **Nitric Oxide (NO)** | ↑ Relaxation of the venous and arterial vasculature. | **Angiotensin II** | ↑ Vasoconstriction |
| | | **Prostacyclin (PGI2)** | ↓ Extracellular volume stimulates. | | |
| | | **Endothelium-derived Hyperpolarizing Factor (EDGF)** | | | |
| | | **Renin** | ↑ Angiotensin I;<br>↑ Angiotensin-converting enzyme activity;<br>↑ Angiotensin II;<br>↑ Aldosterone;<br>↑ Aldosterone release;<br>↑ Reabsorption of sodium and water by the kidneys;<br>↑ Constriction of blood vessels, increasing blood pressure. | **Endothelin-1** | ↑ Vasoconstrictor and modulates vasomotor tone. |
| | | | | **ANP** | ↑ RAAS antagonist. |
| | | | | **Reactive Oxygen Species** | ↑ Vasodilator response. |
| **Sympathetic Nervous System** | | **Inflammatory Signaling** | | **Parasympathetic Nervous System** | |
| **Catecholamines (Noradrenaline/ adrenaline)** | ↑ Blood pressure and peripheral vascular resistance.<br>↑ Positive inotropic and chronotropic effects,<br>↑ Redistribution of peripheral blood volume for maintenance of organic perfusion;<br>↑ Activation of the RAAS system. | **Interleukin-1 (IL-1)**<br>**Interleukin-6 (IL-6)**<br>**Tumor Necrosis Factor (TNF-alpha)** | ↑ Inflammatory status, endothelial dysfunction.<br>↑Intravascular coagulation.<br>↑ Uncoupling of beta-adrenergic stimulus and generation of free radicals. | **Acetylcholine** | ↑ Vasodilation and reduction of heart rate from the decrease in contraction force and cellular metabolism. |
| **Enteric Signaling** | | | | | |
| Activation of guanylate cyclase C receptors | | | | | |
| **Mediators** | | | **Actions** | | |
| **Guanylin and uroguanylin** | | | Promotes natriuresis.<br>Regulates sodium balance.<br>↑ Secretion of water and electrolytes such as sodium, chloride and potassium.<br>↑ Urinary flow.<br>Synergistic effect with ANP. | | |

**Table S2.** Summary of the main biomarkers used in the clinical setting for the analysis of intestinal permeability in the functional, inflammatory, and immunological context. Adapted from Rodrigues and collaborators 2016 (41; doi: 10.5151/9788580391893-18). HPLC: high-performance liquid chromatography; LC-MS/MS: coupled liquid chromatography and the tandem mass spectrometry platform; ELISA: enzyme-linked immunosorbent assay; IIF/ELISA: Indirect immunofluorescence.

| | Biomarkers | Sample | Method | Function | Pathobiological Biomarking |
|---|---|---|---|---|---|
| **Electrophysiological parameters of intestinal epithelial cells** | Specific substrate (glucose, peptide amino acid) marked substance (Cr-EDTA) | Intestinal tissues (duodenum, jejunum, ileum, and colon) | Ussing Chambers | Classic method, widely used to verify in intestinal tissues the bioelectrogenic parameters involved in the absorption of nutrients and permeation, generally associated with the damage processes in epithelial cells. | Various intestinal diseases associated with inflammation and malnutrition among others. |
| **Absorption, permeability, damage and intestinal repair** | % Excretion of lactulose (%L; 342 k Da) | Urine | HPL and/or LC-MS/MS platform | The %L assesses the rise in permeability or the damage to the intestinal epithelium. | %L is linked to diseases that modify the permeability and/or cause damage to the functional gastrointestinal tract barrier. |
| | % Excretion of mannitol (%M; 182 kDa) | Urine | HPL and/or LC-MS/MS platform | %M evaluates the area of intestinal absorption. | %M is linked to diseases that alter the area of intestinal absorption. |
| | Lactulose rate/mannitol (L:M) | Urine | HPL and LC-MS/MS platform | The L:M ratio is used to evaluate the area absorption, injury and functional intestinal barrier repair. | The LM ratio has proven to be a sensitive test for assessing changes in permeability, absorption, and damage to the functional intestinal barrier. |
| | Ileal Fatty Acids Binding Protein (I-FABP; ~13-14 kDa) | Plasma, serum, urine | ELISA | Located in the epithelial cells of the small intestine, it plays a crucial role in the utilization, transport, and metabolism of fatty acids. | This is a biochemical marker indicating that the intestinal cell has been chemically damaged, as evidenced by low levels or absence of I-FABP. |
| | Diamine oxidase (DAO; ~91 kDa) | Serum | ELISA | DAO is produced in the intestinal mucosa and has an inverse relationship with intestinal permeability. | DAO is associated with the integrity of the membrane and the maturity of cells within the small intestinal mucosa. |
| | Litostatine-1-Beta (Reg1β; 19 kDa) | Fecal | ELISA | This protein is synthesized in the crypt cells of the intestine and is involved in tissue repair, cell growth, and proliferation. | The presence of this protein in stool samples indicates the proliferation of crypt cells. |
| **Intestinal Inflammation** | Marked Leukocytes | Fecal | Indium-111-labeled white blood cell scintigraphy | Radiolabeled leukocytes are regarded as the gold standard for detecting inflammation in fecal samples. | This suggests a rise in inflammatory mediators due to increased intestinal permeability. |
| | Alpha-1-Antitrypsin (α-1-AT; 52 kDa) | Fecal, serum | ELISA | α-1-AT is a glycoprotein, acute phase protein and proteinase inhibitor. | Its presence in the fecal sample reflects an increase in intestinal permeability during the inflammatory process. |
| | Alpha 2-macroglobulin (α2M, 820 kDa) | Fecal, Serum | ELISA | This glycoprotein functions as an antiproteinase, with the ability to inactivate a broad range of proteinases. | It regulates inflammatory responses and inhibits the proteolytic activity of trypsin, plasmin, and kallikrein. It is associated with Crohn's disease but not with ulcerative disease. |
| | Lactoferrin (LAF; 80 kDa) | Fecal | ELISA | LAF is found in neutrophil granules and exhibits antimicrobial properties. | A high concentration indicates intestinal inflammation. |
| | Calprotectina (CAP; 36.5 kDa) | Fecal, plasma, serum, urine | ELISA | CAP is a protein that binds calcium and zinc and is part of the S100 protein family. It is produced in neutrophil granulocytes and is also referred to as MRP-8/14, calgranulin A/B, or S100A8/A9. | CAP is present in the cytoplasm of neutrophils, macrophages and eosinophils of ileal tissue. It has antimicrobial, immunomodulatory and antiproliferative effects. It is a potent neutrophil chemotactic factor. |
| | Myeloperoxidase (MPO; 150 kDa) | Fecal, urine | ELISA | MPO is found in neutrophil granules and facilitates the oxidation of substances using $H2O_2$. | The MPO-$H2O_2$ system exerts a toxic effect on microorganisms and serves as an indicator of inflammatory activity within the intestine. |
| | Neopterin (NEP; 253 kDa) | Fecal, plasma, serum, urine | ELISA | NEP is produced and secreted by macrophages and dendritic cells as a result of the cellular immune response to stimulation with IFN-g. | NEP is linked to the activation of the cellular immune response. |
| | Neutrophilic elastase (NE; 29 kDa ) | Fecal | ELISA | It is a serine protease found in the primary granules of polymorphonuclear leukocytes, which are released when neutrophils are activated. | Neutrophilic elastase can dissolve the extracellular matrix and serves as a marker for inflammatory diseases. |
| **Systemic inflammation and immune response** | Anti-neutrophil cytoplasm (ANCA;150 kDa) | Plasma | IIF/ELISA | These antibodies target neutrophil granules and are associated with patients who have ulcerative disease, but not Crohn's disease. | Suggests chronic inflammation linked to heightened intestinal permeability. |
| | Anti-saccharomyces antibodies (ASCA ) | Plasma | ELISA | Similar to the cell wall of enterobacteria, it is associated with patients who have Crohn's | Suggests chronic inflammation linked to heightened intestinal permeability. |

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| | | | | disease, but not with ulcerative disease. | |
| | Liposaccharide (LPS; ~20 KDa) | Plasma, Serum, Homogenized tissue | ELISA | LPS is a toxin produced by bacteria and released into the environment. | Elevated levels of LPS can trigger inflammatory and anticoagulant effects. |
| | LPS-Binding Protein (LBP; 51 kDa) | Plasma, Serum | ELISA | LBP is an acute-phase protein continuously produced by the liver. It facilitates the monomerization of LPS and its subsequent transfer to sCD14 and lipoproteins. | This protein is involved in both activating monocytes through LPS and neutralizing LPS via the lipoprotein pathway. |