Internal and Emergency Medicine (2023) 18:1255–1258
https://doi.org/10.1007/s11739-023-03326-4

EDITORIAL

Raising the curtain: from the gut lumen to human health and disease—the point of interest for internal medicine

Rachele Ciccocioppo[1] · **Piero Portincasa**[2]

Published online: 7 July 2023

Introduction

We welcome the new Topical Collection in *Internal and Emergency Medicine* titled "Gut Inflammation in Human Health and Disease".

Starting from invited reviews and original articles from experts in the field, the Topical Collection will shed the light on several aspects of gut inflammation prone to local and systemic consequences, which are of interest to the large audience of Internists.

The authors will bring the most updated information on pathogenic mechanisms responsible for the disruption of the delicate balance between external factors, the digestive system, and human health. The readers will learn more about several aspects involving inflammatory processes, i.e., gut neutrophils in systemic acute inflammation, gut barrier and mucosal inflammation, gut microbiota in systemic inflammation, neuro-inflammation and gut–brain axis disorders, gut inflammation, and tumorigenesis, as well as gut inflammatory markers and adipose tissue. Additional topics will focus on the links between diet, gut inflammation, metabolic disorders, and pancreatic diseases, as well as bile acid metabolism and gut inflammation, biliary barrier and liver inflammatory stress, and gallstone disease. Importantly, this Topical Collection is a call for further articles addressing the role of gut microbiota, digestive barrier, and inflammation in relation with human diseases.

✉ Rachele Ciccocioppo
rachele.ciccocioppo@univr.it

✉ Piero Portincasa
piero.portincasa@uniba.it

[1] Gastroenterology Unit, Department of Medicine, A.O.U.I. Policlinico G.B. Rossi, University of Verona, Verona, Italy

[2] Clinica Medica "A. Murri", Division of Internal Medicine, Department of Precision and Regenerative Medicine and Ionian Area (DiMePre-J), University of Bari "Aldo Moro", Bari, Italy

To introduce the audience to this wide scenario, this editorial will focus on key aspects of several complex illnesses likely to become pandemic soon, and which will increase the consumption of social, health, and economic resources.

The starting point: from the gut lumen to human health and disease

The epidemiological observation points to the transition of the disease spectrum that occurred during the last century from an acute/infective toward a chronic/degenerative pattern. Other than a critical amelioration of life conditions and diagnostic/therapeutic capacity, this radical change is also attributable to the growing impact of environmental factors on human health. This change has largely contributed to the global burden of complex diseases [1], and depends on an intricate interaction between external factors and individual genetic susceptibility. The interaction not only creates unique molecular pathways leading to tissue injury but also gives rise to the high variability of clinical presentation among patients suffering from the same disorder.

The gastrointestinal tract, with approximately 400 m^2 surface area, represents the largest site of the human body exposed to external factors. Along with its digestive and absorptive functions, the gastrointestinal tract is the main peripheral immunological organ with its gut-associated lymphoid tissue (GALT). Moreover, its lumen and mucosal surface are populated by the gut microbiota, an extraordinary universe of living microorganisms that function as sensors and switchers of mucosal and systemic immunity. Gut microbes continuously adapt their gene expression and composition to external conditions which include, among the others diet and lifestyle, pollution, drugs, smoke, and aging. In the meantime, gut microbes affect local and systemic homeostatic pathways through epigenetic changes of gene expression [1]. The size of this influence depends on the integrity of the digestive barrier/s, complex anatomical and

functional multilevel layers that separate the internal from the external spaces in human body. Both gut mucosa and biliary tree (and possibly the pancreas as well) are endowed with such anatomical–functional structures that not only prevent exogen components to enter but mostly governs the bi-directional exchange of molecules and microorganisms. Alterations of this delicate balance may eventually give rise to chronic inflammatory and metabolic conditions whose prevalence continues to increase steadily in both Western and newly industrialized countries [1].

Changing our approach to disease model

We have been educated to consider a pathological condition as the starting point of a clinical journey. We give that condition a name and make a diagnosis, we try to define a prognosis, and we establish the best therapy. Each pathological condition, however, is the result of a failed health journey. The human body is endowed with an extraordinary functional reserve when tissue damage occurs. The body can adapt to changing environment and masks the pathogenic events until they overcome this resilient capability. This is the point when symptoms and signs of organ injury appear. By studying the molecular pathways involved in the diseased organ, we likely miss few key mechanisms involved in disease initiation and progression. This carries the bias of establishing precise therapeutic targets when analyzing biological samples harvested from diseased organs. This approach may only partially contribute to identifying the whole process whose correction may concretely lead to tissue healing. Indeed, most treatments for chronic diseases display a limited rate of success, often less than 50% which is highly frustrating for health professionals. In this regard, we may mention the case of the therapeutic ceiling effect observed in inflammatory bowel disease (IBD), namely Crohn's disease and ulcerative colitis. Here, despite the growing understanding of disease pathogenesis, the maximum success rate achieved using either old or new therapies, such as biological agents and small molecules, is only about 35% [2], while the failure of drug candidates is over 90% [3]. By implementing new technologies based on omics, bioinformatics, and molecular network analyses in clinical research and mostly by changing our focus from sick to at risk people, we may identify those common determinants of susceptibility to chronic conditions, that eventually may require similar preventive and therapeutic approaches. This dynamic concept of disease modeling represents an epochal change with respect to the traditional reductionistic one [3], and it is expected to have a tremendous impact on internal medicine. It is time to adopt the new concept of 'network medicine' in our research and daily clinical practice to predict individual at risk of disease and design personalized therapies.

Epidemiology of chronic inflammatory conditions

Chronic inflammatory conditions affecting any possible tissue or organ of the human body are lifelong and invalidating conditions. The prevalence is steadily and rapidly increasing in both developed and developing countries and age of onset/diagnosis is mostly in young adults, a condition that largely affects the populations in the productive age [1]. More in depth, data from estimates of levels and trends in disease and injury incidence, prevalence and years lived with disability from 188 countries between 1990 and 2013 showed a critical increase of the percentage change in prevalence of non-communicable, chronic disorders, such as psoriasis (46%), rheumatoid arthritis (57%), inflammatory bowel disease (75%), multiple sclerosis (117%), diabetes mellitus (132%), with the proportion of disability-adjusted life years due to years of lifelong disease increasing globally from 21.1% in 1990 to 31.2% in 2013, and the multi-morbidity increasing with the population aging. This evidence poses the attention on the influence that the Western lifestyle and environment play into the development and maintenance of chronic inflammatory and metabolic disorders. In this regard, the hygiene hypothesis, originally proposed by Strachan [1], provides an explanation for this phenomenon in most industrialized nations. Specifically, the type of child delivery, antibiotic use during childhood, cigarette smoking, air pollution, oral contraceptives, and low levels of vitamin D are considered the main culprits, whereas breastfeeding, having pets in childhood, living on a farm, having a large family, and drinking unpasteurized milk likely play a protective role. In addition, the increasing incidence of these conditions in Europe and the United States since the end of the Second World War coincides with the introduction and massive use of packaged food and fast food chains. In parallel, the consumption of fat, refined sugar, and processed food has increased worldwide, whereas that of fibers has decreased, with most individuals on Western diets do not achieve even the minimum recommended daily intake. The type of food processing plays a role as well. Studies in animal models have shown that food additives, such as saccharin and sucralose, can increase the risk of diabetes, ulcerative colitis, and obesity [4]. Moreover, common emulsifiers can induce low-grade gut inflammation and colitis in experimental animal model [5] while changing the gut microbiota composition and destroying the mucus layer in humans. In this context, microorganisms come in contact and are free to invade the epithelium. The mucous layer is a crucial component of the gut barrier whose disruption represents one of the main

players of gut mucosa inflammation that, in turn, contributes to the pathogenesis of systemic chronic inflammatory conditions. In parallel, the increase in pathobiontic species, indicative of dysbiosis, magnifies and accelerates the onset of mucosal inflammation. This is particularly relevant when occurring in early life, and infants have the highest susceptibility to microbial change in response to environmental factors [6]. Indeed, gut microbial exposure during childhood affects the development of the immune system and mostly of immune tolerance, thus largely contributing to an increased risk of developing immune-mediated disorders later in the life [7]. An overlap of susceptibility genes and their variants, mostly involved in innate and adaptive immune responses, autophagy, intestinal epithelial barrier function, and microbial defense pathways, has been often found among patients suffering from different immune-mediated diseases [8]. It is still unclear, however, why most individuals who carry risk variants remain healthy while others develop one or more chronic inflammatory conditions. The cause, again, may reside in epigenetic modifications that control gene expression and cell response to environmental factors mostly through affecting gut microbiome composition [1].

The pro-inflammatory burden of metabolic disorders

Metabolic disorders, such as type 2 diabetes, nonalcoholic fatty liver disease (NAFLD), and atherosclerosis, are closely associated to insulin resistance, visceral adiposity, overweight, and obesity. The prevalence of type 2 diabetes has risen significantly worldwide over the last decades [9]. The global incidence of diabetes mellitus was 22.9 million in the year 2017, and has a projection to 26.6 million in 2025 [9]. This trend occurs also for NAFLD [10] with a prevalence increasing from 25.5% before 2005 to 37.8% in 2016 [10]. Thus, NAFLD has become the most frequent chronic liver disease worldwide [11, 12]. Obesity has also become a major global health challenge both in adults and in young age [13]. According to the World Health Organization (https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight), obesity has nearly tripled worldwide since 1975. In 2016, more than 1.9 billion adults were overweight, and over 650 million were obese. In 2020, 39 million children under the age of 5 were overweight or obese. In a steato-obeso-atherogenic context, the impact of a local and systemic chronic, low-grade metabolically associated inflammation must be considered in parallel with the increasing risk for cardiovascular disease, neoplasms, and degenerative conditions. We expect huge costs for the health systems worldwide when dealing with chronic non-communicable diseases.

Recent evidence suggests that genetic factors (i.e., the genetic risk depending on nucleotide polymorphisms and predisposing to disease onset and progression) have a little role in determining the epidemics of these disorders. By contrast, as in the case of chronic inflammatory conditions, growing evidence points to a major role of environmental factors as lifestyle, i.e., diet, physical activity, presence of toxic chemical contaminants in food/water, and air pollution. During the last decades, modification in lifestyle and industrial food production, i.e., food management and packaging, global chemical industry, have created worldwide an "obesogenic" and "inflammogenic" environment certainly contributing to the increase of metabolic disorders. In this scenario, in particular, inadequate [14] and widely diffused air pollutants [15] play a critical role. Due to multiple effects on various organs (i.e., brain, heart, liver, pancreas, gut, skeletal muscle, and adipose tissue), these factors are also able to modulate neuronal behavior which control food intake, to change gut microbiota [16], to disrupt gut and liver barriers, to dysregulate signaling pathways to alter gene expression, and to impair modulation of metabolic and gastrointestinal homeostasis, also disrupting signaling pathways and levels of adipokines essential for the metabolic and energetic balance. In this context, the ongoing COVID-19 pandemic has clearly disclosed the complex interplays between infectious and non-communicable diseases, inequities, inequalities, and environmental factors, pointing to the need of wide, multidisciplinary, comprehensive and "one health" approaches to adequately manage the growing epidemics of chronic diseases.

Conclusions and future perspectives

Complex diseases and mostly chronic inflammatory conditions and metabolic-related disorders are expected to become a Public Health burden—whether public or private—in the next future. The conundrum of interactions between genetical, immunological, metabolic, and environmental factors makes hard to establish the appropriate strategies to prevent and treat complex diseases. Nevertheless, the internal medicine community must prioritize research trends and decisions to address this tremendous challenge.

In the modern, post-pandemic era, we must take advantage of technologies to better identify individuals at risk, at all stages of life, and searching for novel biomarkers of susceptibility/development of tissue/organ damage, while addressing new therapeutic interventions. In this Topical collection on gut inflammation, we will pave the way to a better comprehension of concepts like barrier, inflammation, dietary modifications, effect of probiotics and prebiotics, and the interactions between gut microbiota and the immune system, to reduce the global incidence of complex diseases or slow their development. If the concept of "human health" comprises any perturbation of the homeostasis, thus all those

events that precede the establishment of tissue damage and the onset of clinical symptoms and signs deserve our attention. It is time that such hot topics and the concepts of 'gut inflammation' and 'digestive barrier', fully enter the Internal Medicine arena. We urge to increase awareness on the possible origin of main chronic inflammatory and metabolic conditions while searching for novel strategies to prevent the burden of disease and highlighting novel and personalized therapeutic tools.

Declarations

Conflict of interest The authors have no conflicts of interest to declare that are relevant to the content of this article.

Human and animal rights statement and Informed consent Not applicable.

References

1. Strachan DP (1989) Hay fever, hygiene, and household size. BMJ 299(6710):1259–1260. https://doi.org/10.1136/bmj.299.6710.1259
2. Raine T, Danese S (2022) Breaking through the therapeutic ceiling: what will it take? Gastroenterology 162(5):1507–1511. https://doi.org/10.1053/j.gastro.2021.09.078
3. Munos B (2009) Lessons from 60 years of pharmaceutical innovation. Nat Rev Drug Discov 8(12):959–968. https://doi.org/10.1038/nrd2961
4. Suez J, Korem T, Zeevi D, Zilberman-Schapira G, Thaiss CA, Maza O, Israeli D, Zmora N, Gilad S, Weinberger A, Kuperman Y, Harmelin A, Kolodkin-Gal I, Shapiro H, Halpern Z, Segal E, Elinav E (2014) Artificial sweeteners induce glucose intolerance by altering the gut microbiota. Nature 514(7521):181–186. https://doi.org/10.1038/nature13793
5. Chassaing B, Koren O, Goodrich JK, Poole AC, Srinivasan S, Ley RE, Gewirtz AT (2015) Dietary emulsifiers impact the mouse gut microbiota promoting colitis and metabolic syndrome. Nature 519(7541):92–96. https://doi.org/10.1038/nature14232
6. Yatsunenko T, Rey FE, Manary MJ, Trehan I, Dominguez-Bello MG, Contreras M, Magris M, Hidalgo G, Baldassano RN, Anokhin AP, Heath AC, Warner B, Reeder J, Kuczynski J, Caporaso JG, Lozupone CA, Lauber C, Clemente JC, Knights D, Knight R, Gordon JI (2012) Human gut microbiome viewed across age and geography. Nature 486(7402):222–227. https://doi.org/10.1038/nature11053
7. Gensollen T, Iyer SS, Kasper DL, Blumberg RS (2016) How colonization by microbiota in early life shapes the immune system. Science 352(6285):539–544. https://doi.org/10.1126/science.aad9378
8. Zhernakova A, van Diemen CC, Wijmenga C (2009) Detecting shared pathogenesis from the shared genetics of immune-related diseases. Nat Rev Genet 10(1):43–55. https://doi.org/10.1038/nrg2489
9. Lin X, Xu Y, Pan X, Xu J, Ding Y, Sun X, Song X, Ren Y, Shan PF (2020) Global, regional, and national burden and trend of diabetes in 195 countries and territories: an analysis from 1990 to 2025. Sci Rep 10(1):14790. https://doi.org/10.1038/s41598-020-71908-9
10. Riazi K, Azhari H, Charette JH, Underwood FE, King JA, Afshar EE, Swain MG, Congly SE, Kaplan GG, Shaheen AA (2022) The prevalence and incidence of NAFLD worldwide: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol 7(9):851–861. https://doi.org/10.1016/S2468-1253(22)00165-0
11. European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD), and European Association for the Study of Obesity (EASO) (2016) EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol 64(6):1388–1402. https://doi.org/10.1016/j.jhep.2015.11.004
12. Portincasa P (2023) NAFLD, MAFLD, and beyond: one or several acronyms for better comprehension and patient care. Intern Emerg Med. https://doi.org/10.1007/s11739-023-03203-0
13. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, Mullany EC, Biryukov S, Abbafati C, Abera SF, Abraham JP, Abu-Rmeileh NM, Achoki T, AlBuhairan FS, Alemu ZA, Alfonso R, Ali MK, Ali R, Guzman NA, Ammar W, Anwari P, Banerjee A, Barquera S, Basu S, Bennett DA, Bhutta Z, Blore J, Cabral N, Nonato IC, Chang JC, Chowdhury R, Courville KJ, Criqui MH, Cundiff DK, Dabhadkar KC, Dandona L, Davis A, Dayama A, Dharmaratne SD, Ding EL, Durrani AM, Esteghamati A, Farzadfar F, Fay DF, Feigin VL, Flaxman A, Forouzanfar MH, Goto A, Green MA, Gupta R, Hafezi-Nejad N, Hankey GJ, Harewood HC, Havmoeller R, Hay S, Hernandez L, Husseini A, Idrisov BT, Ikeda N, Islami F, Jahangir E, Jassal SK, Jee SH, Jeffreys M, Jonas JB, Kabagambe EK, Khalifa SE, Kengne AP, Khader YS, Khang YH, Kim D, Kimokoti RW, Kinge JM, Kokubo Y, Kosen S, Kwan G, Lai T, Leinsalu M, Li Y, Liang X, Liu S, Logroscino G, Lotufo PA, Lu Y, Ma J, Mainoo NK, Mensah GA, Merriman TR, Mokdad AH, Moschandreas J, Naghavi M, Naheed A, Nand D, Narayan KM, Nelson EL, Neuhouser ML, Nisar MI, Ohkubo T, Oti SO, Pedroza A, Prabhakaran D, Roy N, Sampson U, Seo H, Sepanlou SG, Shibuya K, Shiri R, Shiue I, Singh GM, Singh JA, Skirbekk V, Stapelberg NJ, Sturua L, Sykes BL, Tobias M, Tran BX, Trasande L, Toyoshima H, van de Vijver S, Vasankari TJ, Veerman JL, Velasquez-Melendez G, Vlassov VV, Vollset SE, Vos T, Wang C, Wang X, Weiderpass E, Werdecker A, Wright JL, Yang YC, Yatsuya H, Yoon J, Yoon SJ, Zhao Y, Zhou M, Zhu S, Lopez AD, Murray CJ, Gakidou E (2014) Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 384(9945):766–781. https://doi.org/10.1016/S0140-6736(14)60460-8
14. Kahn LG, Philippat C, Nakayama SF, Slama R, Trasande L (2020) Endocrine-disrupting chemicals: implications for human health. Lancet Diabetes Endocrinol 8(8):703–718. https://doi.org/10.1016/S2213-8587(20)30129-7
15. 1. GBD 2019 Diabetes Air Pollution Collaborators (2022) Estimates, trends, and drivers of the global burden of type 2 diabetes attributable to PM(2.5) air pollution, 1990–2019: an analysis of data from the Global Burden of Disease Study 2019. Lancet Planet Health 6(7):e586–e600. https://doi.org/10.1016/S2542-5196(22)00122-X
16. Di Ciaula A, Bonfrate L, Portincasa P (2022) The role of microbiota in nonalcoholic fatty liver disease. Eur J Clin Investig 52(7):e13768. https://doi.org/10.1111/eci.13768