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To Eat or Not to Eat-An Inflammatory Issue

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Mini Review

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Abstract

Comprised of a rich and complex microbial ecosystem, the human intestinal tract is both an immunological organ and supplier of the body's energy demand and nutrient requirements. This intestinal microbiota provides a large reservoir of bacterial lipopolysaccharide, (known also as endotoxin) that has an immediate stimulatory action on the innate immune system. The gut has evolved mechanisms to detoxify endotoxin and neutralise its potential inflammatory properties. However, this potent inflammatory molecule is transiently detectable in the circulation of healthy individuals following ingestion of food by virtue of a transient gut epithelial permeability arising from the digestive process itself. This acute post-prandial inflammation is somewhat dependent on meal composition with energy rich meals dense in saturated fat and low in fibre and polyphenols exacerbating the process. Chronic exposure to circulating endotoxin by this mechanism has been associated with a dysregulated cardiometabolic phenotype and risk of cardiovascular disease. Spending the majority of wake time in the post-prandial state therefore may contribute to the pathogenesis of these diseases. In this review, I present an overview of the mechanisms by which post-prandial inflammatory events and raise the possibility of modulating meal frequency as a dietary tool to, at least in part, ameliorate the detrimental outcomes of endotoxemia.

Keywords: Inflammation; Epithelial Permeability; Endotoxin; Cardiovascular Disease; Metabolic Syndrome; Microbiome

Introduction

Designed to facilitate digestive function, the gastrointestinal tract forms the largest mucosal interface of the body with the outside world, supplying the body's energy demand and nutrient requirements. However, this anatomical set-up exposes the intestine to a variety of physiological and antigenic challenges. On the one hand, an intact intestinal barrier protects the human organism against invasion of microorganisms and toxins, on the other hand, this barrier must be open to absorb essential fluids and nutrients. Such opposing goals are achieved only by the complex anatomical and functional structure of the intestinal barrier. The term 'intestinal permeability', also known as leaky gut, refers to the functional status of this barrier. The intestinal barrier also has a long history as an immunological organ, hosting more immune cells than any other location in our bodies [1]. Living alongside a microbial ecosystem, these potential combatants are actually collectively responsible for a wide array of critical immune-regulatory tasks. Thus, the intestinal barrier is complex and multi-layer both physical and functional, immune and microbial.

Falling Through the Cracks

Appropriate fluctuations in permeability of the intestinal epithelium is a functional feature crucial for the balance between nutrient absorption during ingestion of a meal and microbe exclusion from the underlying lamina propria. A scaffold of tight junctions (TJ) including zonulins, occludins, claudins and junctional adhesion molecules modulate movement from intestinal lumen to bloodstream. Digestion itself negatively affects TJ assembly, increasing gut permeability and permitting the transient presence of low doses of pro-inflammatory bacterial compounds into the blood, termed endotoxemia caused by Lipopolysaccharide (LPS, also known as endotoxin), a component of the gram-negative bacterial cell wall translocating the epithelial barrier. Endotoxin has an immediate impact on the activation of the distil innate immune system via Toll-like receptors leading to intracellular activation of nuclear factor factor-□B (NF-□B), systemic inflammatory cytokine release (including Tumour Necrosis Factor-□ - TNF□, Interleukin-1 - IL-1 and interleukin-6 IL-6) which participate in the pathogenesis of epithelial barrier dysfunction and trigger release of acute phase proteins (including C-reactive protein - CRP and Serum Amyloid A - SAA) by the liver [2,3]. The mechanisms of these postprandial inflammatory responses are exaggerated by lipaemia and increased chylomicron formation and triacylglyceride (TAG) content in circulation. Chylomicron and TAG adherence to, and activation of, monocytes further provokes the immune response [4,5]. Interestingly, TAG levels increase from baseline in a similar pattern to endotoxin over a four-hour post-prandial period but despite higher baseline, TAG levels did not increase significantly in metabolically compromised over healthy individuals.

Acute by Design

Digestion in and of itself is an inflammatory process producing endotoxemia and low-grade inflammation by virtue of epithelial permeability and microbial products translocating to the blood where they switch on inflammatory events [6]. Inflammation is acute by design. In healthy adults, the majority of post-prandial inflammatory cytokine events are short-lived, detected as early as one hour after a meal and remaining elevated for up to four hours [7,8]. Acute phase SAA and CRP follow quite different kinetics with almost no detectable increase up to five hours before a slow rise to peak at around 24 hours. While this is a normal physiological phenomenon, an energy rich 'western-style' diet significantly increases this mechanism and data are now accumulating that emphasise the importance of epithelial barrier integrity to minimising LPS translocation to overall health [9,10]. High fat intake has also received particular attention in induction of epithelial permeability. Not only do high fat diets encourage gram negative bacteria at the expense of gram positive, but endotoxin has a strong affinity for chylomicrons (lipoproteins that transport dietary lipids including long-chain saturated fatty acids (SFAs) through the gut wall) and, as such, can cross the gastrointestinal mucosa coupled with damaging lipoproteins [11,12]. Thus, fat intake may induce endotoxemia via enhanced intestinal absorption related to chylomicron formation. However, it has also been suggested that total energy intake, rather than fat intake per se, confounds these previous observations [13]. The 'leaky gut hypothesis' explains how frequent or inappropriate intestinal barrier permeability is associated with the incidence of disease including cardiometabolic diseases, type two diabetes and other inflammatory and autoimmune syndromes [14,15]. Efforts to identify sources elevating systemic inflammatory tone have implicated gut-derived endotoxin as a trigger [7]. This has led to the common assumption that such conditions may reflect a chronic low-level LPS driven activation of the systemic innate immune system [16,17]. Unlike higher doses of serum LPS such as those seen in the case of sepsis, post-prandial low level circulating endotoxin has little impact on malaise and temperature while retaining more subtle inflammatory features [18-20]. It should be borne in mind that the majority of studies evaluating endotoxemia are done in the fasted state thus the kinetics of experimentally induced endotoxemia could differ from the post-prandial physiological state coming from a meal. In addition, means used to assess permeability can vary widely and have been reviewed elsewhere [9,21].

Regulation by Mouth & Microbes

To counter the various dietary barrier disruptors, extensive epithelial TJ networks are dynamically regulated by a diverse array of protective factors many of which recruit the use of the cacophony of bio-active compounds in the diet, the microbiome themselves and their metabolites. Short chain fatty acids (SCFA), the microbial fermentation products of dietary fibre are one well documented example [22,23]. These end-products of microbial fermentation facilitate tight junction assembly and stimulate the production of intestinal alkaline phosphatase involved in regulation of chylomicron transport and detoxification of endotoxins [24,25]. More recently, Vitamin D has been shown to modulate tight junctions [26]. Finally, polyphenols, natural plant derived metabolites known to exert various anti-inflammatory

and antioxidant benefits, as recently shown by Yang et al. to have a beneficial effect on the epithelial barrier integrity [27]. Polyphenols are considered to exert their protective effects on the epithelial barrier by targeting different members of the NF-?B family and antagonising subsequent pro-inflammatory cytokine production that cause TJ disassembly. *In vitro*, naringenin, a major polyphenol in citrus fruits and curcumin, a major polyphenol in turmeric enhanced tight junction formation and barrier integrity and in vivo, countered chemically induced gut epithelial damage [28-30]. Grape seed extract (GSE) that contains a mixture of polyphenols reduced endotoxemia in experimentally induced compromised barrier integrity and promoted the mRNA expression of TJ proteins [31]. In addition, resveratrol, a polyphenol extracted from grape seed and skin, promotes the mRNA expression of TJ proteins [32]. The role of NF-κB in the impairment of the intestinal barrier is further supported by treatment with the NF-κB inhibitor pyrolidinedithiocarbamate [33]. Piegholdt reported the isoflavonebiochaninA improved TEER in NF-κB/TNF-α induced disruption of barrier integrity *in vitro* [34]. Sirtuin 1 (SIRT1) is a NAD^+-dependent protein deacetylate that sense environmental stress to alter intestinal integrity. SIRT1 has recently gained attention due to its association with increased longevity and as a protective upregulated by fasting [35]. Resveratrol, an agonist of SIRT1, alleviates TNF-α induced TJ Zonulin-1 disturbances leading to epithelial permeability in the gut [36].

Meal Frequency as a Health Modulator

Data assessing reduced meal frequency without calorie restriction have found little or conflicting impact on traditional cardiometabolic parameters such as body weight, plasma lipids or glucoregulatory factors [37,38]. Moving beyond traditional cardiometabolic parameters to the inflammatory process itself has only recently garnered significant investigative support. Consequently, there is a paucity of information on the effects of dietary intervention to markers of inflammation in cardiometabolic patients [39]. Considering low-grade inflammation may be acting upstream of traditionally assessed cardiometabolic risk factors, modification of meal frequency has potential to make an immediate and easily implementable clinical management tool particularly for obesity where current therapeutics are limited and offer only modest improvements. Obese women who changed their diet from multiple daily meals to alternate-day restriction exhibited significant reductions in levels of circulating TNFα and IL-6 [40]. However, moving upstream to inflammatory markers such as IL-6 and CRP is also complicated by ongoing controversy regarding their causal role and challenges in measurement due to circadian variation and dietary post-prandial effects [41-43]. With the knowledge that metabolically 'at risk' individuals show exacerbated endotoxaemic responses, advising more frequent meals, even if they are smaller, has potential to allow endotoxin to spike several times per day thus precipitating low-grade inflammation without desensitisation. Resulting downstream production of inflammatory and acute phase molecules would be in continuous production, as previous in vivo and in vitro studies have demonstrated [44-49]. This cumulate effect may actually exacerbate their inflammatory risk regardless of dietary content or energy balance but would be further aggravated in those consuming a high fat, low fibre/polyphenol content with gut dysbiosis.

Although known for quite some time, post-prandial epithelial permeability and consequential endotoxemia has yet to translate into a dietetic approach. The UK National Institute for Health and Care Excellence (NICE) advise a Mediterranean style diet based on a body of epidemiological, physiological and observational evidence demonstrating that such changes in diet are associated with reductions in morbidity and mortality from cardiovascular disease [50,51]. Current guidelines on meal frequency are often entangled with calorie reduction strategies [52]. For example, current recommendations for type 2 diabetics is to consume five small meals a day, presumed as a strategy to reduce hunger and therefore total energy intake although there are no clear insights into the supporting evidence. Kahleova et al. reported eating two larger meals as more effective than six smaller meals [53]. Observational trials in human indicate that eating more frequently than three times per day may play a role in obesity [54]. Other studies stress the division of food intake should be frequent but based on individual preference, with no clear recommendations on number of meals. As new data now demonstrates, society has crept towards a continual snacking routine and we now spend the majority of waking time in a post-prandial state [55]. Understanding the contribution of meal frequency and its acute and cumulative effects on inflammatory risk therefore warrants further investigation since leaving frequency to preference may not be beneficial, particularly in at risk populations.

Though studies have correlated increased eating frequency with increased body weight, what is not yet clear is how spending significant periods in the post-prandial state impacts metabolic risk in healthy adults cumulatively over a long-period of time [56,57]. What we

do know is that reduced frequency of eating through intermittent fasting (IF) and time-restricted eating (TRE) is an important aspect of eating frequency that claims to have broad effects on human health span and offers an innovative strategy to prevent and treat metabolic disease [58,59]. Restricting the food improves metabolic profiles but data from humans are limited. Mice under time-restricted feeding given equivalent energy intake from a high fat diet as those with ad libitum access are protected against obesity and metabolic abnormalities [60,61]. In addition, eating aligned with the diurnal circadian pattern of humans attenuates metabolic disease arising from a variety of obesogenic diets proportional to fasting duration and maintained even when temporarily interrupted [58]. Cyclical changes in the gut microbiome resulting from diurnal feeding and fasting rhythms contribute to the diversity of gut microflora and represent a mechanism by which the gut microbiome affects host metabolism. An extended fasting period (i.e., gut rest) could also lead to reduced gut permeability and upregulation of SIRT1, as a result, blunt postprandial endotoxemia and systemic inflammation [62-64]. Whether via IF, TRE or reducing the number of meals, we cannot ignore that dietary eating patterns impact health and disease [65]. Spending a large portion of time out-with the post-prandial state offers both a potential preventative and therapeutic intervention against diverse cardio-metabolic health challenges. Diet is not the only factor to cause barrier permeability and barrier permeability is not the only contributor to low grade systemic inflammation [66]. An individual's risk of inflammatory disease result from the interplay of many factors including social, environmental and genetic contributions. At a time when inflammation is a unifying theme of the many lifestyle and age related diseases that are rapidly increasing in prevalence, medicine is moving toward modifiable lifestyle-based paradigm.

Conclusion

History is teaching us that it is an unhelpful reductionist tendency neither to pit individual causative dietary constituents against each other nor to discount the medications and procedures used as treatments. Ultimately, a meal is the sum of its parts, by studying centrality of dietary patterns and behaviours, away from isolated nutrient and energy intake, the minutia of individual dietary constituents become less relevant. While the role for saturated fat in cardiovascular disease remains heavily debated, there is no doubt that saturated fat can exacerbate dietary perturbations to the endothelium further facilitating LPS transfer via chylomicron formation [67-76]. Nor is there any dispute over continuing to promote the key role of lifestyle interventions such as regular exercise and consuming a fibre, nutrient and polyphenol dense diet for good cardiometabolic health and reducing unruly inflammation. But as the majority moving towards spending the majority of waking time in a post-prandial state cumulatively promote the inflamed state, reduced meal frequency may be preventative in nature with the benefits accruing over lifespan rather than prescribing a change in eating pattern after a diagnosis.

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