

## REVIEW ARTICLE

# Autonomic nervous system in adolescents with inflammatory bowel disease, immunity, and exercise

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## Abstract

Physiological anti-inflammatory mechanisms represent well-organized systems that have been developed by evolution to control inflammation. The autonomic nervous system (ANS) dysfunction may contribute to the development and maintenance of chronic inflammatory illnesses including inflammatory bowel diseases (IBD). The central nervous system obtains sensory inputs from the immune system through both humoral and neuronal routes. Inflammatory input activates an anti-inflammatory reaction that promptly inhibits overproduction of inflammatory cytokines. The ANS moderates gastrointestinal motility, secretion, permeability and mucosal immunity. Besides the sympathetic nervous system, the parasympathetic nervous system, in addition to its typical function of hormone secretion, controlling heart rate, gastrointestinal peristalsis, and digestion, may also be involved in the control of the immune reactions to commensal flora and alimentary constituents. It is now well recognized that cholinergic enteric neurons participate in epithelial transport and mucosal immune defense. In IBD, changes in enteric autonomic regulation may also influence neural cardiovascular control. Whether this dysfunction results from the inflammatory component of these illnesses or it is a primary cause, has not yet been satisfactorily answered. Several studies have examined the effects of exercise on the immune function. Some of them have shown that moderate and regular exercise has a significant role in the prevention and treatment of many diseases. Physical activity is inversely correlated with systemic low-level inflammation, suggesting that regular exercise may provide beneficial health effects in the patients with chronic illnesses like IBD. The protective and anti-inflammatory effects of exercise may be mediated by muscle-derived peptides called myokines. The reverse association of physical fitness with the IBD risk is consistent with a protecting role of exercise. The literature shows that very few patients receive advice from healthcare professionals regarding exercise.

## INTRODUCTION

Pediatric inflammatory bowel diseases (IBD) are challenging illnesses from medical as well as psychological, and behavioral viewpoints. The symptoms, including diarrhea, abdominal pain, rectal bleeding, fatigue, growth failure, and postponed puberty, present unique psychosocial challenges for the sufferers (Mackner *et al* 2006). This is especially true in adolescents, who make up the majority of diagnosed pediatric cases (CCFA 2009). They must face learning to manage a chronic illness; that is hard to debate with others, while trying to preserve a typical teenage life and fulfill developmental tasks. Treatment of IBD is multifaceted regarding the number of medications and their fluctuating dosing schedules. The episodic, variable, and unpredictable disease exacerbations often lead to more or less temporary permanent changes of medication.

Since some supportive therapeutic interventions could improve the course of the illness, it is important to understand the aspects of the etiopathogenesis of IBD. One of the interesting areas is the role of ANS dysfunction that may contribute to the development and maintenance of chronic inflammatory processes. In view of the fact the ANS functioning might be improved (for example by regular exercise, relaxation or meditation, or by using medication at the time of onset of the illness), the overall course of the disease could be improved as well. This article deals with the problems of the ANS dysfunction in IBD and its influence on the immune system and with the possibilities to improve it.

## AUTONOMIC NERVOUS SYSTEM IN CHRONIC DISEASES

The autonomic motor system involuntarily controls visceral functions. The two branches of the autonomic nervous system – the parasympathetic and the sympathetic – uninterruptedly regulate basic physiological responses, such as heart rate and blood pressure, respiratory rate, gastrointestinal motility, and body temperature (Elenkov *et al* 2000; Rosas-Ballina *et al* 2008). The autonomic nervous system obtains signals from specialized sensory receptors to detect actual physiologic status, such as baroreceptors to monitor blood pressure and stretch receptors and chemoreceptors to monitor gastric movement (Lucini *et al* 2002; Moak *et al* 2009). The primitive brain, including the limbic system, brain stem, and hypothalamus, receives signals from these receptors and coordinates sympathetic and parasympathetic neural responses to maintain cardiovascular homeostasis or regulate digestion (Saeed *et al* 2005).

## AUTONOMIC NERVOUS SYSTEM AND IMMUNITY

Physiological anti-inflammatory mechanisms represent capable systems that have been developed and perfected by evolution to control inflammation (Pellissier *et al*

2010). Inflammatory stimuli activate (exacerbate) afferent pathways within the vagus nerve that are relayed to the hypothalamus. Inflammatory input activates an anti-inflammatory reaction that promptly inhibits overproduction of inflammatory cytokines. The central nervous system (CNS) creates/directs the inflammatory response (Lindgren *et al* 1993). It collects information about inflammatory or invasive events from multiple local sites, mobilizes defenses, and creates a memory trace to improve the chances of survival in future. Sensing peripheral inflammation, CNS obtains sensory inputs from the immune system through both humoral and neuronal routes (Blalock 1994). IL-1 $\alpha$ , TNF, and other immunological mediators can gain access to the brain centers that are devoid of blood–brain barrier, known as circumventricular regions. Also, the mediators can penetrate other parts of the brain by active transport systems. IL-1 $\beta$  and endotoxin may activate afferent vagus nerve signals, leading to a typical sickness behavior, including food aversion and fever (Maunder *et al* 2006). Both the humoral and neuronal routes from the immune system to nervous system communication play its role in the development of fever, anorexia, activation of hypothalamic-pituitary responses to infection and injury, and other behavioral manifestations of illness.

## HEART RATE VARIABILITY AND AUTONOMIC NERVOUS SYSTEM

Heart rate variability (HRV) is a term that describes rapid reactions of the cardiovascular control systems, namely, the sympathetic and parasympathetic branches of the autonomic nervous system (Pagani *et al* 1997). Continuous variations in the sympathetic and parasympathetic neural impulses on the sinoatrial node exhibit alterations in heart rate and cause oscillations of the R–R interval around its mean value (i.e. HRV). Increasingly sophisticated calculations have been developed to measure HRV. The most commonly used method to quantify HRV oscillations is the linear spectral analysis. This conventional method is known to be an attractive tool for the detection of the autonomic instabilities in various clinical illnesses (Berntson *et al* 1997). The spectral analysis can offer information about physiological mechanisms influencing three frequency bands – high frequency (HF), low frequency (LF), and very low frequency (VLF). The currently most significant issue lies in the interpretation of these frequency bands according to the function of branches of the ANS system – sympathetic and parasympathetic. There are strong propositions that the HF represents parasympathetic activity (Task Force 1996), but we must be careful in the understanding of the LF and VLF frequencies. Several authors (Malliani *et al* 2005; Pagani *et al* 2009) proposed that the LF represents the activity of sympatheticus, but actual investigation shows, that this is not so clear. Other studies suggest that the LF band represents both sympathetic and parasympathetic activity (Moak *et al*

2009; Goldstein *et al* 2011), especially because of the baroreflex activity. Other factors also influence the LF – e.g. central oscillator, vasomotor noise. The physiological explanation of the VLF frequency is equivocal as well. It is hypothesized VLF to be under the impact of thermoregulation, peripheral vasomotor and the rennin – angiotensin – aldosterone system.

## **NERVUS VAGUS, INFLAMMATION, AND GUT SYSTEM**

The inborn immune system is essential in the first reactions to invading pathogens. When confronted, the host needs an adequate inflammatory reaction but also strives to prevent collateral damage to tissues due to the extreme systemic range of inflammation and discharge of the inflammatory mediators. Hence, the regulation of the acute inflammatory reaction is necessary, and regulatory mechanisms are needed to accomplish this. Many years ago, the sympathetic nervous system was already identified as a “hard-wired” counterregulatory mechanism that can locally regulate immune responses (Elenkov *et al* 2000).

Besides the sympathetic nervous system, the parasympathetic nervous system within the vagus nerve is increasingly recognized as an influential player in neuroimmune inflammation. The vagus nerve, in addition to its typical function of hormone secretion, controlling heart rate, gastrointestinal (GI) peristalsis, and digestion may also be involved in the control of the immune reactions to commensal flora and alimentary constituents (Altschuler *et al* 1991, 1993; Borovikova *et al* 2000). The structure of the afferent vagus system is recognized to control the inflammatory reaction via stimulation of the hypothalamic-pituitary-adrenal axis (Pavlov *et al* 2006). Nevertheless, more recent evidence tells that the efferent vagus nerve cholinergic activity exerts a quite strong immunomodulatory potential as well (Borovikova *et al* 2000). Immune cells that have been shown to be particularly sensitive to modulation by vagus nerve activity are macrophages (Borovikova *et al* 2000). Macrophages express nicotinic acetylcholine receptors (nAChRs) and powerfully respond to acetylcholine (ACh). Classical neurotransmitter ACh also functions as a neuro-immune cytokine, providing a molecular basis for the purported “neuro-immune axis” between the brain and the immune system (De Jonge *et al* 2005). As the ACh signals through nicotinic or muscarinic receptors, selective agonists and antagonists were used to recognize the receptors involved in the immunomodulatory effects of ACh. Nicotine was as effective as ACh in inhibiting pro-inflammatory cytokine production in macrophages, showing that the anti-inflammatory effects of ACh on immune cells are intermediated through nAChR, rather than muscarinic receptors. The nAChR  $\alpha 7$  subtype, which is expressed on immune cells, is essential for mediating the anti-inflammatory effect of ACh (Wang *et al* 2003).

Tracey (2007) postulated that the cholinergic anti-inflammatory pathway may act as a part of an anti-inflammatory reflex arch. In the arch, the manifestation of pro-inflammatory cytokines in the periphery stimulates vagus afferents and results in the vagus efferent firing. This subsequently leads to an attenuation of cytokine release from macrophages via nAChR  $\alpha 7$  (Tracey 2007). On the other hand, recent data indicate that the efferent arm of the cholinergic anti-inflammatory pathway may, at least in part be mediated via postganglionic events (Rosas-Ballina *et al* 2008). Neuronal tracing studies show that the efferent vagus nerve fibers innervate the small intestine and proximal colon of the gastrointestinal tract (Altschuler *et al* 1991, 1993). That leaves the opportunity that cholinergic activity modulates the immune cells residing in, or recruited to the densely innervated bowel wall. In investigational models of acute colitis, the vagus nerve seemed to show regulatory properties in inflammatory responses. Several studies displayed that nicotine administration diminishes disease in TNBS and DSS colitis models, although fairly high doses of nicotine are required (Eliakim *et al* 1998; Sykes *et al* 2000). To sum it up, cholinergic activation can reduce inflammation and disease activity in various animal models of intestinal inflammation, likely via a mechanism involving activation of nAChR  $\alpha 7$  subtype, although this receptor may not be the sole nAChR involved.

It is now well recognized that cholinergic enteric neurons participate in epithelial transport and mucosal immune defense. The intestinal epithelium is continuously exposed to an overabundance of luminal antigens (Savage 1977). The intestinal immune system has to fight attacking pathogens while continuing of the tolerance of the beneficial flora and the numerous encountered antigens in food. Under healthy circumstances, specialized cells, such as M-cells or CX3CR positive dendritic cells, expand through the epithelial layer of normal mucosa or Peyer’s patch and act as gatekeepers to the mucosal immune system (Niess *et al* 2005). Nevertheless, the penetration of the mucosal barrier by luminal antigens does happen under pathological conditions, and the regulatory mechanisms of epithelial permeability are critically important to/for the balance between immunosurveillance and inflammation of the gut. For illustration, in episodes of stress, inflammation or trauma, impairment of the epithelial barrier function is increasingly recognized as an important perpetuating factor in the pathogenesis of IBD, food allergy and celiac disease (DeMeo *et al* 2002).

Many hypotheses stand up about the controlling mechanisms behind these permeability changes (Xavier & Podolsky 2007), but interestingly, several investigators specify that the cholinergic nerve activity shows a substantial role in gut permeability. Saunders *et al* (1994) showed that rodents demonstrate that both acute and chronic exposure to stress can enlarge epithelial permeability via the cholinergic mechanisms.

First of all, the stress susceptible rats have lower activity of cholinesterase in the intestinal mucosa than the less sensitive rats, leading to the higher levels of mucosal ACh, which may account for the altered epithelial barrier function in the stress-susceptible rats (Saunders *et al* 1997). Secondly, the cholinergic muscarinic receptor antagonist atropine closes down the stress-induced epithelial barrier damage in rats, where nicotinic antagonists have no effect. This suggests that the cholinergic effects on epithelial barrier function are mediated via muscarinic, rather than nAChRs.

Several lines of evidence show that vagus nerve stimulation can inhibit immune cell activation and modulate inflammation via its peripheral release of ACh. Many reports point towards the macrophage nAChR  $\alpha 7$  as an essential player in mediating the anti-inflammatory effect of ACh (Wang *et al* 2003; De Jonge *et al* 2005; van Westerloo *et al* 2006; Giebelen *et al* 2007; Pavlov *et al* 2007; Parrish *et al* 2008). Specifically, nicotine exerts anti-inflammatory effects on human macrophages that can be counteracted by specific nAChR  $\alpha 7$  antagonists or antisense oligonucleotides (Wang *et al* 2003).

The finding that nicotine inhibits activation of immune cells, together with the observation that vagus nerve signaling or specific nAChR  $\alpha 7$  agonists attenuate disease in several inflammatory animal models, implies that therapeutic agents modifying cholinergic signaling might be important also in humans.

We recently discovered that cholinergic neurons can regulate TNF synthesis via ACh (Borovikova *et al* 2000; Wang *et al* 2003). Called the 'cholinergic anti-inflammatory pathway,' because ACh is the principle parasympathetic neurotransmitter, macrophages exposed to ACh are efficiently neutralized. Experimental stimulation of the cholinergic anti-inflammatory pathway by direct electrical activation of the efferent vagus nerve inhibits the synthesis of TNF in liver, spleen, and heart, and decreases serum TNF levels during endotoxaemia, ischaemia/reperfusion injury, haemorrhagic shock, and other diseases related to excessive cytokine release (Bernik *et al* 2002; Guarini *et al* 2003, 2004). Vagotomy significantly exacerbates TNF responses to inflammatory stimuli and sensitizes animals to the lethal effects of endotoxin, suggesting that the anti-inflammatory cholinergic signals transmitted via the efferent vagus nerve play a role in maintaining immunological homeostasis (Borovikova *et al* 2000; Bernik *et al* 2002).

Macrophage expression of the  $\alpha 7$  subunit of nicotinic ACh receptor distinguishes the cholinergic anti-inflammatory pathway from muscarinic receptor activities identified previously on lymphocytes, peripheral blood mononuclear cells, and alveolar macrophages (Sato *et al* 1999). Activation of the macrophage ACh receptors inhibits endotoxin-induced NF- $\kappa$ B signaling but does not affect the stimulation of several mitogen-associated protein kinases typically related to endotoxin signaling (Wang *et al* 2004). The finding that the macrophages are exquisitely sensitive to ACh suggests

that other non-neuronal cells that produce ACh (e.g. epithelial cells, T-lymphocytes, endothelial cells) may also participate in modulating the function of adjacent tissue macrophages (Kawashima & Fujii 2000).

Most studies to date characterizing the cholinergic anti-inflammatory paths have concentrated on the macrophage-ACh interaction, but other cell types, predominantly the endothelium, are also potentially regulated by ACh. The activation of endothelial cells during inflammation, described by increased adhesion molecule expression and inflammatory mediator production, plays an essential role in the adhesion and subsequent transferring of inflammatory leucocytes. Inflammatory mediators, such as chemokines, existing on the surface of the endothelium progressively stimulate leukocytes rolling across the vasculature. For example, neutrophils become activated by binding to the endothelium-expressed adhesion molecules (Ley 2002). Microvascular endothelial cells express the  $\alpha 7$  subunit of the ACh receptor on the cell surface, and ACh considerably blocks TNF-induced adhesion molecule expression and chemokine expression in a concentration-dependent manner (Saeed *et al* 2005). ACh also modifies the intestinal inflammatory responses and decreases histamine release by airway mucosal mast cells (Reinheimer *et al* 2000).

It is now legitimate to propose the hypothesis that dysfunction of the cholinergic anti-inflammatory pathway may predispose some individuals to the excessive inflammatory responses (Pavlov *et al* 2006). The cholinergic anti-inflammatory pathway typically provides a brake on the immune system that restrains cytokine production (Saeed *et al* 2005). If this becomes deficient, either due to insensitivity to ACh released by the pathway or due to weakened signals in the pathway, cytokine responses can become excessive.

## AUTONOMIC NERVOUS SYSTEM AND INFLAMMATORY BOWEL DISEASES

The ANS moderates gastrointestinal motility, secretion, permeability and mucosal immunity. The dysfunction of ANS may be of pathogenetic importance in IBD. The ANS, especially the parasympathetic system, modulates the immune response in the chronic inflammatory disorders. The autonomic dysfunctions have been reported earlier in the patients with IBD; however, the results have been conflicting (Sharma *et al* 2009; Dogan *et al* 2011; Yorulmaz *et al* 2013). Lindgren *et al* (1993) used three reliable non-invasive tests constructed on the heart reactions to deep breathing (expiration/inspiration ratio) and tilt (acceleration and brake index) in patients with biochemically inactive ulcerative colitis. The authors then compared with the results of the healthy controls, the irritable bowel syndrome patients, and the Crohn's disease patients. The individuals with ulcerative colitis had a significantly lower expiration/inspiration ratio than controls in age-corrected values,

indicating vagal nerve dysfunction in contrast to a predominantly sympathetic dysfunction in Crohn's disease. The patients with Crohn's disease and ulcerative colitis demonstrated high percentiles in the respiratory sinus arrhythmia test when compared to controls (Straub *et al* 1997). Autonomic hyperreflexia was significantly related to more severe inflammation and systemic disease in IBD. Hyperreflexia may be a response to inflammation or a pathogenetic element that drives mucosal inflammation. In our study (Jelenova *et al* 2015) HRV as a possible marker of chronic distress in adolescents with IBD was compared to HRV frequencies in the healthy adolescents. The participants were 29 adolescents with IBD (nineteen with Crohn's disease and ten with ulcerative colitis), 25 patients were in remission and 4 presented mild disease activity. They were compared with the control group of 35 healthy children of the same age (13–16 years old). In the HRV assessment, the patients with IBD had significantly lower levels of the spectral activity in the LF band in all three positions of the orthostatic test; reduced levels of the VLF in both supine positions; and the ratio of the spectral activity at LF/HF was statistically significantly lower in the second position (standing).

In IBD, changes in enteric autonomic regulation may also influence neural cardiovascular control. Nevertheless, while cardiac autonomic modulation has been presented to be impaired in active ulcerative colitis, the occurrence of the cardiovascular autonomic alterations, also in the latent phase of IBD, remains an unanswered question. Thus, the aim of Coruzzi's *et al* (2007) study was to explore the features of autonomic cardiovascular regulation in ulcerative colitis and Crohn's disease during remission phase. Autonomic cardiovascular control was measured by time- and frequency-domain indexes of natural heart rate and blood pressure variability and by measuring the baroreflex heart rate control (sequence technique) in 26 ulcerative colitis patients, 26 Crohn's disease patients, and 23 healthy controls. The groups had equal mean levels of blood pressure and variability. By contrast, the average heart rate, its overall variability (standard deviation), and baroreflex sensitivity were lower in the patients with ulcerative colitis than in the healthy controls. Additionally, all indexes related to the cardiac vagal control were significantly lower in the patients with ulcerative colitis with respect not only to controls but also to the patients with Crohn's disease. The cardiac vagal control was weakened in quiescent ulcerative colitis only, and not in Crohn's disease, although in both bowel diseases vascular control appeared to be preserved. Since cardiovagal modulation seems to be related to anti-inflammatory mechanisms, the reduced parasympathetic cardiac regulation in apparently quiescent ulcerative colitis suggests, that such systemic derangement is accompanied by local subclinical inflammations, even in the absence of clinically active inflammatory processes. Sharma *et al* (2009) assessed the autonomic functions in the patients

with IBD in clinical remission. Heart rate variability (HRV), which included time-domain, frequency-domain, and nonlinear indices (Poincaré plot), was assessed using Nevrokard, version 6.4.0 Slovenia, in 118 patients with IBD (ulcerative colitis: n=62, Crohn's disease: n=56, and 58 healthy controls). There was no significant difference in the mean of R-R intervals in the patients with ulcerative colitis, Crohn's disease, and the healthy controls. The frequency domain indices (the absolute values of total power, the high-frequency power, and the low-frequency power) were lower in the patients with ulcerative colitis and Crohn's disease vs. controls. The high-frequency was statistically significantly decreased in the ulcerative colitis patients compared to the healthy controls. There was no significant difference in the low-frequency and the LF/HF ratio in the ulcerative colitis and Crohn's disease patients and healthy controls. Among the Poincaré plot indices, while the standard deviation of the instantaneous R-R interval variability was lower in the ulcerative colitis and Crohn's disease patients vs. healthy controls, and there was no significant difference in the long-term R-R interval variability. The patients with IBD display decreased ANS functions. The patients with ulcerative colitis have a significantly lower parasympathetic function in comparison to those with Crohn's disease and healthy controls. These autonomic dysfunctions in the patients with IBD may have a significant influence on the pathogenesis of IBD.

Yorulmaz *et al* (2013) investigated the frequency and factors of prolonged QT dispersion that may lead to severe ventricular arrhythmias in the patients with IBD. The study involved 63 ulcerative colitis and 41 Crohn's disease patients. Forty-seven healthy individuals were included as the controls. Heart rate was measured using electrocardiography, corrected QT dispersion (QTcd) and the Bazett's formula. The IBD patients had more prolonged QTcd in comparison to the controls.

Patients with autoimmune diseases, including rheumatoid arthritis, diabetes, and lupus, experience a dysfunction of the autonomic nervous system, as evidenced by a variety of tests including tilt table responses (Tan *et al* 1993; Gamez-Nava *et al* 1998; Huynh *et al* 1999; Meyer *et al* 2004). Other inflammatory diseases, including Crohn's disease, are also associated with the autonomic dysfunction (Straub *et al* 1997; Ellenby *et al* 2001). This dysfunction has been extensively ascribed to secondary complications of nerve inflammation leading to suppressive signaling; other mechanisms have also been proposed. A new view of the cholinergic anti-inflammatory pathway leads to an alternative explanation: it is possible, that dysfunction of this pathway is a proximal or even first event that allows the overproduction of cytokines in response to different mild stimulus (Saunders *et al* 1997; Tracey 2007). Current clinical studies focussing on this hypothesis are in development, and the results will provide further insight into the pathogenesis of autoimmune diseases.

Clinically, the autonomic dysfunction has been connected with the inflammatory illnesses such as Crohn's disease, lupus, diabetes, rheumatoid arthritis, and sepsis. Whether this dysfunction is the consequences from the inflammatory component of these illnesses, or is a primary cause, has not yet been satisfactorily answered. Loss of HRV, a reflection of autonomic dysfunction, is also associated with increased sepsis mortality (Landry *et al* 1997; Yien *et al* 1997; Arons *et al* 1999).

The recognition that the cholinergic anti-inflammatory pathway represents an evolutionarily conserved and potent endogenous pathway to protect the host from its immune response is an exciting new finding in general/theoretical and clinical immunology (Ulloa 2005). Extracellular nucleotides and their receptors have been involved in the pathogenesis of the IBD. T-lymphocytes are thought to play a primary role in the induction of epithelial cell damage in IBD, and the P2Y6 receptor was induced to be highly expressed on the T cells infiltrating the diseased segment, but lacking in T cells of the unaffected bowel. This means that P2Y6 receptor and its selective agonist, UDP, may play a role in the pathogenesis of IBD. P2Y6 receptors are involved in the monocytic release of interleukin-8 and stimulation of NaCl secretion. During inflammation of the gastrointestinal tract, glial cells proliferate and produce cytokines; thus, P2X7 receptors may play a part in the response of enteric glia to inflammation. (Vanderwinden *et al* 2003). Functional expression of the P2X7 receptor in the colonic macrophages and T lymphocytes in the mucosa of IBD suggests they may play a role in the immunopathology of the disease (Li *et al* 2001).

## IMMUNITY AND EXERCISE

Physical activity has been established to improve health-related quality of life in several patient populations with a chronic illness. In the recent years, studies have shown the role of physical stress on the immune system. These studies have examined the effects of exercise on the immune function (Nieman 1997, 2000). Some of them have shown that moderate and regular exercise has a significant role in the prevention and treatment of many diseases (Malm 2004; Pedersen and Nieman 1998). Investigation of the effects of exercise on the immune function encompasses a broad range of sporting activities including short-term, exhaustive activity, endurance and long-term activities, and regular light exercise (Tofighee *et al* 2014). Changes in the immune factors were found to be dependent on the type of physical exercise implemented on a regular basis. Bearing in mind the protective antibody response in those performing regular sports, a moderate exercise carried out on a regular basis could be considered to affect positively mononuclear and polymorphonuclear phagocytic cells – the fundamental elements of the natural immune system (Saygin *et al* 2006). It is broadly accepted that acute and chronic exercise alters the number and func-

tion of circulating cells of the innate immune system (e.g. neutrophils, monocytes, and natural killer cells) (Walsh *et al* 2011).

On the other side, it has been reported that high-intensity long term training in elite athletes may increase the risk of the immune function (Suzuki *et al* 2003; Lee *et al* 2015). There are the indirect markers of the cellular immune system suppression by intensive exercises and stimulation of IgG production by moderate exercises (Buyukyazi *et al* 2004).

Mueller *et al* (2001) showed that immune system in adolescents may profit from moderate endurance training by an increased capacity to generate IFN-gamma while the immunity following repeated exhausting exercise of competitive athletes tends to deteriorate through down-regulation of IFN-gamma and IL-12.

Limited evidence advocates that exercise may have beneficial, anti-inflammatory effects in patients with IBD (DeFilippis *et al* 2016). As in other chronic diseases, muscle function peak power and peak oxygen uptake are reduced in IBD patients (Wiroth *et al* 2005; Ploeger *et al* 2011). Furthermore, up to date, no negative side effects of moderate exercise on the physical condition of the IBD patients have been observed to date (Bilski *et al* 2014).

The importance of exercise as an adjunct therapy has been proposed for the patients with IBD (Bilski *et al* 2014; Ng *et al* 2006; Pérez 2009; Narula & Fedorak 2008). Small studies have shown that exercise may be well tolerated in patients with a mild disease course (Martin 2011; Loudon *et al* 1999; Ng *et al* 2007). There are concerns that exercise may exacerbate symptoms in the patients with IBD. Depending on the intensity and duration, exercise may induce a transient mild systemic inflammation and increased level of cytokines leading to an exacerbation of gastrointestinal symptoms (Bilski *et al* 2014). However, limited evidence suggests that consistent moderate exercise is beneficial for the IBD patients. Even the patients with moderately active IBD are capable of performing the symptom-free regular exercise (Klare *et al* 2015). Moderate exercise down-regulates inflammatory cytokines such as interleukin-1 and tumor necrosis factor alpha (Bilski *et al* 2015). Furthermore, the patients with IBD have reported that exercise had positive effects on their mood, fatigue, weight maintenance, and osteoporosis (Nathan *et al* 2013).

Physical activity is inversely correlated with systemic low-level inflammation, suggesting that regular exercise may provide beneficial health effects in the patients with chronic diseases like IBD (Bilski *et al* 2014; Kasapis & Thompson 2005). Long-term voluntary exercise may decrease the expression of pro-inflammatory cytokines like TNF-alpha and apoptotic proteins such as caspase-7 (Packer & Hoffman-Goetz 2012). Regular exercise also improves psychological health by reducing stress and anxiety, which may help to minimize disease activity since increased stress levels are associated with recurrence of active disease (Packer *et al* 2010).

The protective and anti-inflammatory effects of exercise may be mediated by muscle-derived peptides called myokines (Pedersen & Febbraio 2012). Contracting skeletal muscles release myokines such as interleukin-15, which may directly mediate anti-inflammatory effects. Similarly, creeping fat present in the patients with Crohn's disease consists of mesenteric white adipose tissue (Kredel *et al* 2013). This tissue is composed of macrophages and T-lymphocytes in addition to adipocytes, which release various inflammatory factors such as cytokines and chemokines (Kredel *et al* 2013; Jung *et al* 2013; Bilski *et al* 2013). This mesenteric fat is associated with increased tumor necrosis factor alpha and correlates with the severity of intestinal inflammation (Bilski *et al* 2014; Jung *et al* 2013). The myokines and adipokines suggest potential cross-talk between skeletal muscle and adipose tissue (Pedersen & Febbraio 2012; Bilski *et al* 2013).

Physical fitness may diminish systemic inflammation levels relevant to the risk of symptomatic Crohn's disease and ulcerative colitis (Melinder *et al* 2015). Authors assessed whether fitness in adolescence is associated with subsequent IBD risk, independent of risk markers and prodromal disease activity. The reverse association of physical fitness with the IBD risk is consistent with a protecting role of exercise (Melinder *et al* 2015). However, evidence of disease activity before diagnosis was already present in adolescence, suggesting that some or all of the associations between fitness and IBD may be due to prodromal disease activity reducing exercise capacity and, therefore, fitness. Although they may advantage from exercise, the IBD patients, experience considerable barriers to regular exercise secondary to the relapsing and remitting nature of IBD (DeFilippis *et al* 2016). Still, the patients suffering from moderately active IBD are capable of performing symptom-free regular endurance exercise. Klare *et al* (2015) support the assumption that physical activity is beneficial for the IBD patients. Physical activity may furthermore improve the quality of life through improvements in social well-being, and may, therefore, be a useful adjunct to IBD therapy. The literature shows that very few patients receive advice from healthcare professionals regarding exercise (Nathan *et al* 2013). Thus, most patients determine their amount and intensity of exercise based on their energy level. The multidisciplinary gastroenterology team including stoma nurses should be involved in these consultations to help patients manage swimming and other forms of exercise (Nathan *et al* 2013).

## PHARMACOLOGY MODULATION OF IMMUNITY IN IBD

Tobacco smoking is the main environmental feature to provoke IBD, and excessive smoking has distinctive influences in the ulcerative colitis and the Crohn's disease. While smoking escalates the risk of developing

Crohn's disease and worsens its course, epidemiological studies of smokers with ulcerative colitis point out that smoking appears to have a protective effect on the development of this disease and reduces its severity (Lakatos *et al* 2007). The exact clarification for this inconsistency remains unclear, but it certainly supports the current belief that ulcerative colitis and Crohn's disease are two distinct illness entities. About 90 % of the ulcerative colitis patients are non-smokers. The patients with a history of smoking may develop the disease after cessation of smoking (De Jonge *et al* 2007). The patients, who smoke intermittently, often experience improvement in their colitis symptoms during the periods when smoking (Van Assche *et al* 2005; Pullan *et al* 1994). In the ex-smokers, the onset of the illness is almost constantly after give up smoking. Nevertheless, clinical studies using nicotine for the treatment of ulcerative colitis have provided different outcomes. Transdermal nicotine seems to be superior to placebo for the initiation of remission in the patients with ulcerative colitis, but no significant benefit for transdermal nicotine treatment matched to standard medical treatment was found.

Additionally, adverse events related to transdermal nicotine are important as they limit its usage in patients (McGrath *et al* 2004). However, to avoid side effects caused by nicotine, more specific nAChR agonists are considered. Partial selective nAChR  $\alpha 7$  and  $\alpha 4\beta 2$  agonists are already being tested in patients with neuronal disorders, and both receptor subtypes have shown to mediate improvement in attention, learning, and working memory (Cincotta *et al* 2008). The use of particular  $\alpha 7$  nicotinic agonists is anticipated to have a potential as a maintenance therapy for the active ulcerative colitis. Such selective nicotinic agonists were originally designed to mimic the cognitive effects of nicotine in the patients with neurological disorders while avoiding the toxicity of nicotine (Ulloa 2005; Kitagawa *et al* 2003). Between these, the most typical is GTS-21, a partial  $\alpha 7$  nAChR agonist that also affects  $\alpha 4\beta 2$  nAChR (Kitagawa *et al* 2003; De Jonge *et al* 2007). Besides these selective agonists, recent evidence indicates that centrally acting cholinergic drugs used in the treatment of Alzheimer disease can modulate peripheral immune responses and would, therefore, be interesting for further exploration (Pavlov *et al* 2006).

## CONCLUSIONS

Autonomic dysfunction has been connected to the human inflammatory diseases including IBD. The cholinergic nervous system decreases the production of proinflammatory cytokines and inhibits inflammatory processes. The regular physical exercise is one of the behavioral factors that can influence the immune function. People suffering from moderately active IBD are capable of doing symptom-free regular exercise. The adolescents with IBD seem to be able to implement

running and walking without experiencing clinically meaningful adverse effects on intestinal and general health. The regular physical activity is a useful complementary therapy tool that is capable of improving the quality of life and well-being in the patients suffering from mildly active IBD.

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