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The anti-inflammatory effects of exercise in the syndromic thread of diabetes and autoimmunity

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Abstract. – A unifying thread over the wide spectrum of diabetes might be the triggering of innate immunological and inflammatory pathways leading to insulin resistance, β-cell dysfunction and β-cell destruction: the hybrid features of type 1 and type 2 diabetes. In fact, hyperglycemia can arise from a deficit in insulin action, insulin secretion, or both.

Regularly exercising at moderate intensity has been shown to efficiently and positively impact upon physiological imbalances caused by several morbid conditions. Even in different immunological dysfunctions, physical exercise has been prescribed as a complementary therapeutic strategy. In fact, as suggested by our observations, there is a putative inverse relationship between autoimmunity markers (GAD, IA) and exercise-derived energy expenditure in type 1 pre-diabetic subjects. Exercise also has been shown to maintain muscle mitochondrial function and thus ability to maintain fuel metabolism and islet cell function. An additional benefit is the enhancement of antioxidant defense system and thus reducing oxidative stress.

Therefore, the purpose of this review is to address the importance of physical exercise in a broad range of metabolic disorders that set out a common milieu in which type 1 and type 2 diabetes could be identified as one extensive syndrome.

Key Words:
Inflammation, Exercise, Immunometabolism, Diabetes, Autoimmunity, Cytokines, Adipokines, Myokines.

Introduction

The anti-inflammatory effects of exercise against new-era metabolic diseases have been debated for a long time, yet the causative mechanisms for this are far to be clearly ascertained. The continuing rise in prevalence and incidence of low-grade chronic diseases such as diabetes, obesity and the related cardiovascular diseases (CVD), for which aerobic moderate-intensity exercise has been shown to be protective, poses a threat worldwide especially considering the healthcare costs that these diseases entail. It has been estimated that physical inactivity causes 6-10% of all deaths from the major non-communicable diseases (coronary heart disease, type 2 diabetes, and breast and colon cancer) and it is responsible for premature mortality by 9%, or more than 5.3 of the 57 million deaths that occurred worlwide in 2008; which is equal to stating that physical inactivity causes as many deaths as tobacco does globally[1,2].

In the last decades much evidence has been accumulated documenting the many health benefits of physical activity: regular exercise offers protection against all-cause mortality, primarily by lowering the atherogenic profiles[3], reduces rates of CVD, hypertension, metabolic syndrome, type 2 diabetes, breast cancer and colon cancer. Furthermore, physical training has been proved to be effective in the treatment of several of these diseases, including ischemic heart diseases[4] and heart failure[5].

While it has been known for a long time that physical exercise induces glucose-lowering effects by increasing insulin sensitivity and thus represents a cornerstone in the therapy and prevention of type 2 diabetes, it is still uncertain whether exercise could be potentially beneficial (and to which extent) in type 1 diabetes. Indeed, regular exercise in people with type 1 diabetes does not necessarily lead to improved glycemic control, and sustained execise requires great care to adjust insulin administration and carbohydrate intake[6,7]. However, ongoing observations indicate that subjects with type 1 diabetes who follow a regular schedule of aerobic training have prolonged "honeymoon" – the early stage of the disease in which insulin requirements are lower than in ad-

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vanced type 1 diabetes. Once precised, exercise may have a role beyond its insulin-mimetic action, therefore reducing the autoimmune response that in type 1 diabetes attacks and destroys the β insulin-producing cells. Recent studies have suggested that physical exercise may interfere with immune system function even at low intensity and duration: it has been prescribed as a complementary therapeutic strategy even in different immunological dysfunctions[8]. Moreover, modern environmental factors including high-calorie and proinflammatory diets, sedentary lifestyles in sanitized indoor environments, vitamin D insufficiency, might be activating innate immune responses promoting "hybrid" forms of diabetes[9]. The available evidence indicates that, in fact, impaired insulin secretion (β-cell dysfunction) is also a feature of type 2 diabetes, and insulin resistance is also a risk factor for the development of type 1 diabetes[10]. The incidences of both types of diabetes have considerably increased over the past half century in the developed world, regardless of any definitional features, like age. "Double diabetes" has been referred to individuals who have both autoimmunity against β-cells and insulin resistance [11,12]. Children, adolescents and adults with these hybrid forms of diabetes often report a family history of both type 1 and type 2 diabetes, central obesity, and weaker immunogenetic markers than those with classic type 1 diabetes (i.e. lower-risk HLA genes, etc.)[11]. We detected autoimmunity markers in 10% of people with type 2 diabetes in our database[13].

In this perspective, physical exercise would enable the achievement of better positions on the glucose-tolerance curve by ameliorating insulin sensitivity in every subject, either with type 2 or type 1 diabetes (Figure 1). Traditionally, physical exercise has been promoted in type 2 diabetes where insulin action is deficient in the context of insulin resistance and/or inappropriate insulin secretion. However, even in type 1 diabetes, in the dysregulation of immune system function, beta-cell toxicity is mediated by a complex interplay between oxidative stress and inflammation, for which exercise could be protective[14].

Given its powerful ability to modulate oxidative stress and protect against chronic inflammatory conditions, like those leading to autoimmunity diseases, we want to review how favourably exercise might affect these syndromic features in the modern diabetogenic environment.

Inflammetabolic Stress for Insulin-Producing β-cells

A considerable amount of evidence couples type 1 and type 2 diabetes: even though they may have diverse etiological and pathogenetic paths, similar end-lines, such as pacreatic β-cell apoptosis and failure, may concern both diseases in humans[15,16]. Insulin dependence in fact may be eventually occurring in both types, featured by a peculiar time and rapidity of manifestation. Several concepts and drivers have been proposed in the last 2 decades in order to characterize and classify the stereotypes of diabetes[9,10]. However, an overlap of conditions and scenarios imposes a proper understanding of the mechanisms so as to guide both treatment and prevention of diabetes, and to deal with its ultimate consequence of clinical relevance: the insulin deficiency.

A vast array of situations in fact threathen the functionality of the β-pancreatic mass, leading the insulin-producing islets to their final demise, i.e. the β–cell failure: increased stimulation of the β-cells due to overfeeding; obesity; insulin resistance; psychological stress; infections; low physical activity; and all the modes promoting islet inflammation and metabolic stress/unbalance. It is possible that all these inflammetabolic stressors stimulate or sometimes even initiate the autoimmune β-islet disturbance[17] (Figure 1).

Pancreatic islets of patients with type 2 diabetes exhibit signs of metabolic stress and inflammation, containing more macrophages and secreting higher levels of interleukin (IL)-1β, IL-6, IL-8, and MIP (macrophage inflammatory protein)-1α than normal islets[15,18]. Augmented pancreatic islet inflammation has been confirmed in type 2 diabetic subjects by elevated expression of other inflammatory cytokines derived from innate immune cells, such as TNF-, IL-12, other than IL-1β[19]. Hence, β-cell function might be impaired by innate immune mechanisms, leading to β-cell failure, even in type 2 diabetes. However, studies found an increased prevalence of islet-associated antigen-specific antibodies and T-cell responses in type 2 diabetic patients (targeting autoantigens like GAD65, IA2, proinsulin)[20,21]. Additionally, a recent work reported an elevated presence of B cells within islets of type 2 diabetic individuals[19]. These latter findings support a putative islet-specific adaptive immune process in type 2 compared with healthy control subjects.

In summary, a broad scenario of β-cell stress including lipotoxicity, glucotoxicity, endoplasmic reticulum stress, chronic inflammation (derived

from obesity, insulin resistance or both) is supportive for a positive correlation between islet autoimmunity and reduced β-cell function and -mass seen in type 2 diabetic patients[22,23]. However, the underlying mechanisms behind this are presently unclear.

The exercise-effects on the cytokine response that may be anti-inflammatory and offer protection to β-cell against all these insults are envisaged. Depending on intensity, type and duration, physical exercise is a potent inducer of physiological changes at different levels, pertaining stress hormones, energy crisis and oxidative stress. These exercise-related modifications, and possibly adaptations, may be responsible for a favourable inflammatory cytokine pattern and may preserve the β-cell redox homeostasis – and thus its insulin secreting capacity – against the multiple-origin attacks directed towards β-cells (Figure 1).

Adipose Tissue and Inflammation

Across all the aforementioned conditions, certainly diabetes and obesity represent the hallmarks of the derangements in the complex interplay between metabolic and immune processes.

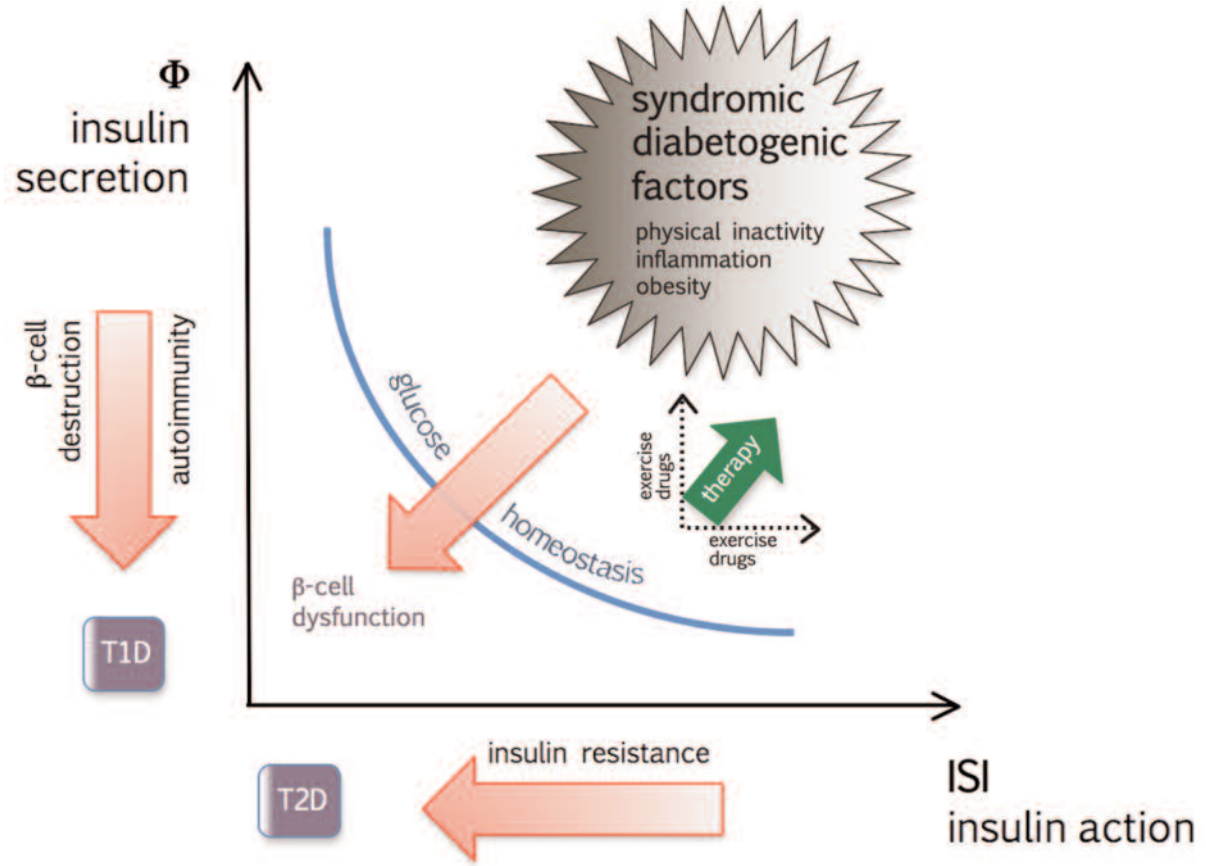

Figure 1. Environmental syndromic thread affecting glucose homeostasis. The relationship between insulin sensitivity and beta-cell function is hyperbolic. When the homeostatic ability of the glucose-insulin system is healthy, changes in insulin sensitivity (ISI) tend to be compensated by changes in beta-cell secretion (ϕ) of opposite sign. This means that, by riding the "hyperbola", glucose homeostasis can be preserved with a reduction in insulin sensitivity that corresponds to an augmented insulin secretion. If this does not occur, a growing insulin resistance *(left-handed red arrow)* might be leading to type 2 diabetes. Conversely, a not-compensated insulin secretion, perhaps owing to autoimmunity attacks *(downward red arrow)*, might progressively destroy β-cell mass, resulting in type 1 diabetes. However, environmental multiple-differentiated attacks (syndromic diabetogenic factors, in the spined diagram) can unhealthly drag glucose homeostasis to the β-cell dysfunction area, upon the triggering of both axes (ϕ, ISI). The green therapy vector, as a resultant from a potentially combined strategy of exercise and drugs, counteracts all these diabetogenic factors towards an ameliorated glucose tolerance area. Actually, according to our observations, physically exercise alone may be helping individuals in two way by both enhancing insulin sensitivity (increasing insulin action) and β-cell function (through the reduction of the deleterious effects of autoimmunity). The two effects are likely to combine together and produce a substancial gain in glucose tolerance. Potentially, they may even delay the onset of frank diabetes.

Inflammation, in a chronic low-grade systemic mode, appears as a common denominator of several pathologies[24]. Quite recently, fascinating studies proved that obesity and diabetes are associated with markers of activated innate immune system and inflammation: chronic, low-grade inflammation has been detected in multiple tissues of obese individuals[25], especially when obesity is exacerbated by the additional diagnosis of diabetes[26,27].

Although the ethiology is matter of debate, it probably implies the activation of cellular stress responses via super-abundant lipid accumulation within key-cells such as adipocytes or hepatocytes[28-30]. Excessive hepatic lipid accumulation is known to be linked to hepatic insulin resistance, hepatosteatosis and liver inflammation (both in obesity-induced and not-) via multiple deleterious mechanisms[31,32]. Adipocytes are recognized as crucial sites in the generation of inflammatory responses and mediators: here, a group of peptide hormones and cytokines, named "adipokines"[33], are produced and secreted to regulate fuel use and lipid storage in other peripheral tissues. Among proinflammatory adipokines, TNF-α is a potent activator of various signal trasduction cascades, including those as critical inhibitors of insulin action: the discovery of elevated levels of TNF-α in obese mice provided the first evidence that subclinical inflammatory processes accompany insulin resistance and metabolic dysfunction, anticipating type 2 diabetes[34]. Expanded adipose tissue is associated with heightened production of other proinflammatory adipokines such as IL-6, retinol-binding protein-4 (RBP4), IL-18[33]. Conversely, amounts of adipokines with anti-inflammatory functions, like adiponectin, are found reduced in accumulated adipose tissue compared with the proinflammatory ones[33]. Leptin is another regulatory hormone released by adipocytes into the circulation, acting as "anti-diabetogenic", by influencing the hypothalamus to control appetite[35,36]. Intriguingly, this extended immunometabolic framework can be triggered and modulated by physical exercise.

In adipocytes, chemokines and cytokines may work in network upon diverse metabolic stimulation and may even interact with other effectors of the immune system, including immune cells, like T-cells, macrophages and dendritic cells[37]. It has been documented that, in adipocytes, metabolic stress elicits the release of MCP-1, a chemoattractant cytokine which regulates migration of circulating monocytes to adipose tissue and promotes their differentiation into adipose tissue macrophages[30,38].

Akin to macrophages, T and B cells – autoreactive species of adaptive immune response – were found to infiltrate visceral adipose tissue in obese humans[39] and mice[40,41]. Moreover, in DIO (diet-induced obesity)-mice, T- or B-cell depletion or genetic deficiency resulted to ameliorate insulin resistance, confirming a tight thread surrounding adaptive immunity, obesity-related inflammation and insulin resistance[40-43].

The addictive involvement of all these cell types (both innate and adaptive immune cells) in metabolic homeostasis opens an appealing research area yet to be fully explored – the immunometabolism[44] – and raises the possibility that obesity-related insulin resistance and -inflammation may have a defined autoimmune component[45].

It has been shown that exercise is capable of modifying structure, inflammatory- and immune responses in visceral and subcutaneous adipose tissue[46]; therefore it emerges as substantial intervention to blunt, harness, counteract (and possibly revert) all this cluster of immunometabolic disturbances and, to some extent, even when autoimmune-based.

The challenge would be to understand how large is this therapeutical window for the beneficial effects of exercise.

Skeletal Muscle and Inflammation

Similarly to adipose tissue, a parallel analysis can be made for the skeletal muscle, recently advocated as a proper endocrine organ, giving its secretory capacity to release several proteins, cytokines and even hormone-like mediators[47]. These factors exert specific endocrine effects within the muscle cells themselves or on distant organs too. Put in this way, skeletal muscle may produce hundred of "myokines" via paracrine, autocrine, endocrine mechanisms to modulate signalling pathways either locally or by releasing these proteins into the circulation directly[48].

Considering that the majority of the adipokines are proinflammatory, myokines secreted by muscle fibres could balance the harmful adipokine-mediated effects typical of (or leading to) chronic diseases. In fact, upon contraction, skeletal muscle may produce several proteins – altering the so-called "myokine response" – and therefore physical activity could

represent a potential defense against proinflammatory modes. In addition, miokynes may target other organs, thus, a new explorable crosstalk arises not only between skeletal muscle and adipose tissue but also with liver, pancreas, bones and brain (Figure 2). Taken together, these observations raise the question of what are these myokines, and specifically, which of them are exercise-induced/modulated to counteract inflammation. A novel paradigm on how skeletal muscle communicates with other organs has to be addressed.

A great deal of interest has been given to myostatin, one of the first muscle factor described as "myokine". Secreted into the circulation, myostatin is a robust growth-inhibitor and, as such, its deletion promotes skeletal muscle hypertrophy[49] along with its elected inhibitor, follistatin. This latter might be referred as "hepatokine", since it is released from the liver to regulate muscle expression of myostatin in relation to exercise. Follistatin proves the existence of a possible crosstalk between muscle and liver, during and following exercise[50]. Myostatin is also involved in the maintainance of metabolic homeostasis and modulation of adipose tissue function and mass[51-54]. Increased muscle and circulating levels of myostatin were found in obese individuals[55]. Myostatin inhibition decreases adiposity and ameliorates muscle weakness[56]. Endurance and resistance exercise lower myostatin expression in humans and rodents[57].

IL-6 has been recognized as a myokine prototype, given its master role in immuno- and inflammatory-modulating metabolism in response to muscle contractions[48]. Depending on intensity,

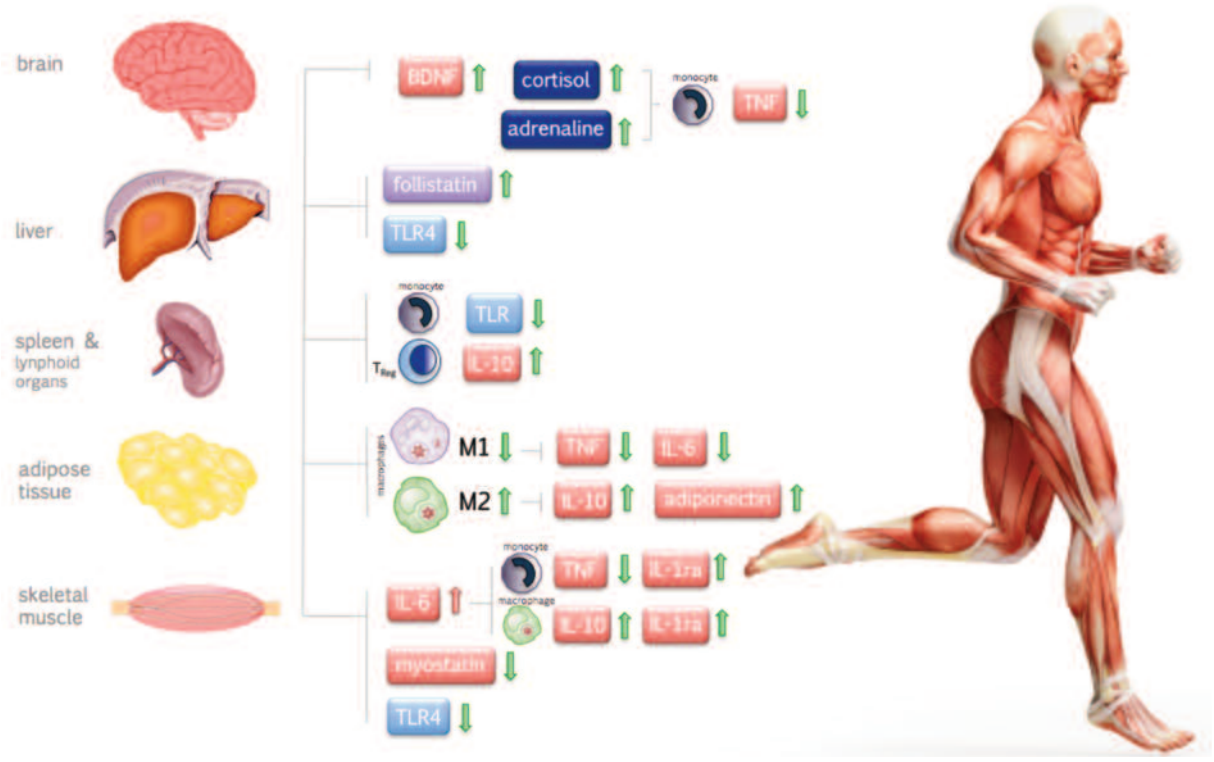

Figure 2. Organ exercise-mediated crosstalk contributing to the anti-inflammatory pattern. Multiple organs are affected by exercise, initiating diverse anti-inflammatory responses. In the brain, the hypothalamic-pituitary-adrenal axis is activated and it induces adrenal cortex and medulla to produce cortisol and adrenaline, respectively. These two hormones, in turn, suppress the release of the proinflammatory tumor necrosis factor (TNF)-citokines by monocytes. Protein and mRNA expression of follistatin, another member of TNF-superfamily, are markedly increased in the liver following exercise to inhibit myostation action. In other organs and tissues (liver, spleen, muscle) exercise can also lower the expression and the activation of Toll-like receptor 4 (TLR4), thereby reducing adipose tissue infiltration and other proinflammatory cytokines. In adipose tissue, a switch from M1 to M2 macrophage phenotype may inhibit the release of the proinflammatory cytokines – interleukin-6 (IL-6) and TNF – and increase the production of anti-inflammatory cytokines, such as IL-10 and adiponectin. IL-10 may be also upregulated by the increased circulating numbers of regulatory T cells (T_{reg}). Contracting muscles are responsable for a complex cascade which ultimately results to be anti-inflammatory: increases in IL-6 determine a downregulation of TNF as well as an upregulation of IL-10 and IL-ra.

duration of exercise, rescruited mass, one's endurance capacity, circulating levels of IL-6 increase in an exponential fashion [58]. Muscle cells are the primary source of IL-6 during exercise, although IL-6 may have systemic effects on the liver and adipose tissue and it increases insulin sescretion via up-regulation of GLP-1[59,60]. Through AMPK activation, IL-6 enhances insulin-stimulated glucose uptake both in skeletal muscle and adipose tissue, and it increases lipid oxidation locally (intra-muscle) and whole-body[61,62]. BDNF (brain-derived neurotrophic factor) is also involved in muscle AMPK-mediated fat oxidation[63] and its circulating levels increase with aerobic exercise, especially with high-intensity exercise[64]. In the brain, BDNF increases neuronal connections and is crucial for some aspects of memory[65]. Plasma transient appearance of IL-6 following exercise is of paramount relevance because it induces the production of the anti-inflammatory cytokines IL-1ra, and IL-10[66]. Importantly, skeletal muscle production of IL-6 during exercise inhibits, the release of proinflammatory cytokine TNF-α, independently[67]. As energy sensor, IL-6mRNA expression and protein content are inversely correlated with carbohydrate availability; specifically they are increased as the intramuscular glycogen levels are low[68]. Other potential roles of IL-6 are stimulation of muscle growth[69,70] and angiogenesis[71]. A myriad of studies on the involvement of IL-6 in the pathogeneses of obesity, insulin resistance, type 1 and type 2 diabetes, confirm the great expectations from IL-6 as a candidate physiological mediator of β-cell protector[14,60,72-74], possibly via exercise[47].

IGF-1 and FGF-2 are involved in bone formation[75]. Irisin is a myokine discovered to have a role in "browning" of white adipose tissue, i.e. in driving brown-fat-like development of white adipose tissue, with high favourable metabolic significance[76].

Despite its anabolic and anti-catabolic effects, mainly by diminishing lipid deposition, IL-15 cannot be reported as a true myokine, since studies describing its secretion from muscle cells are lacking[48]. However, muscle-derived IL-15 has been advocated as one of the mediators of the anti-obesity effects of exercise[77].

If skeletal muscle cells were found to possess a "humoral" factor more than 50 years ago[78], a new vista of a branched-out muscle crosstalk with other organs requires increasingly sophisticated approaches to understand the critical nodes of immuno- and energy metabolism. Future exercise-studies could yield transformative research outcomes in these areas, and hopefully unveil how these pathways are disrupted in a number of inactivity-related diseases.

The Anti-Inflammatory Effects of Exercise

Physical exercise is generally prescribed, together with diet and drugs, in type 2 diabetes therapy because of its well-established glucose-lowering effects and insulin-mimetic actions. However, exercise may be pleiotropic and counterbalance proinflammatory cytokines activity, impacting significantly on both immunoregulation and non-immune events in many cell types and tissues outside the immune system.

Exercise and autoimmunity. We collected immunological and metabolic data in patients with type 1 diabetes (male n=6; female n=6; BMI 24.6±1 kg/m^2; 46±4.9 years, mean and SE) and analyzed them with energy expenditure data, assessed by a seven-day physical activity self-completed diary, to understand whether exercise could favourably affect autoimmunity: a regression results analysis showed an inverse relationship between autoimmunity markers (GAD, IA) and weekly energy expenditure (EE) derived from physical exercise[13]. In addition, type 1 diabetic subjects with higher physical activity index than their peer-controls were found to have a prolonged "honeymoon-period", and reduced exogenous insulin requirements, respectively. This period of time in the course of diabetes onset has been seen to last as long as 10-15 years in some athletes. These observations suggest that exercise may positively modulate immune system function. In a retrospective analysis[79], 10-year followed-up subjects with type 1 diabetes showed ameliorated scores of disease management and quality of life.

Furthermore, our studies showed that physical activity may be helping and preventive for β-cells transplanted recipients by counteracting diabetic symptoms and mitigating the side effects of immunosuppressive drugs and graft dysfunction[80]. In fact, in these patients, progressive insulin resistance might be a probable outcome of immunosuppression and chronic inflammation.

According to other studies[14], the anti-inflammatory effect of exercise mediated by upregulation of Th2 cytokines may even lead to a protective response against the autoimmune process directed to β-cells.

M2-M1 shift in adipose tissue. In inflammed adipose tissue, like in obesity, there is a shift in the immune cell profile[81]. Resident M2 anti-inflammatory macrophages decrease while M1 proinflammatory macrophages increase. A preferential recruitment of M1-type macrophages has been associated with the initial state of inflammation in adipose tissue[82]. This state precedes both local and systemic insulin resistance. Inflammation can be hence attenuated by chronic exercise in high-fat fed mice, both with reduced macrophage infitration and a switch from an M1 to an M2 macrophage phenotype.

IL-6. Along with the reduction of visceral fat mass, and subsequently via a decrease in proinflammatory adipokine secretion, another exercise anti-inflammatory mechanism can be ascribed to the release of IL-6 from contracting muscles. Literature is overwhelmed by studies on IL-6, nevertheless its role remains contorversial[83]. IL-6 itself is a proinflammatory acute-phase cytokine and its plasma concentrations were seen elevated in subjects with impaired glucose tolerance[84-86]. High plasma levels of IL-6 are also associated with physical inactivity[87] and metabolic syndrome[88]. However, IL-6 mediates a number of anti-inflammatory responses: the transient rise in circulating levels of IL-6 during exercise (up to 100-fold in response to it)[89-91] stimulates the appeareance in the blood stream of the anti-inflammatory cytokines IL-10 and IL-1ra and the release of cortisol from adrenal gland[66]. This hormone, in turn, as well as adrenaline, inhibits the release of proinflammatory cytokine TNF-α by monocytes[92] (Figure 2). IL-6 itself downregulates the production of TNF-α as indicated by *in vitro* and animal studies[93-95].

IL-1ra. IL-1ra belongs to the IL-1 family and it is primarily produced by monocytes and macrophages. It inhibits the proinflammatory actions of IL-1β[96]. While IL-6 levels tend to peak at the cessation of exercise, circulating levels of IL-1ra are modestly heightened at the end of exercise and then increase remarkably in the hours following exercise[66]. This confirms the fact that IL-6 is a major inducer of IL-1ra. IL-1β is a master cytokine, controlling local and systemic inflammation: its plasma levels are increased in a vast number of metabolic diseases[97].

IL-10. IL-10 plays an important role in orchestrating an anti-inflammatory reaction, especially by activating macrophage and monocytes. It inhibits the production of several proinflammmatory chemokines like IL-1β, IL-1α, TNF- α, IL-8, therefore, compromisig the inflammatory capacity of effector T cells[98,99]. Ultimately, IL-10 downregulates the adaptive immune responses and minimizes inflammation of damaged tissues[98]. Circulating levels of IL-10 were found low in obese subjects[100].

CRP. Some longitudinal studies have showed that regular exercise training induces a reduction in C-reactive protein (CRP)[101,102], a sound marker of systemic low-grade inflammation (Table I). CRP has a role both in induction of anti-inflmmatory cytokines in circulation monocytes, and in suppressing the synthesis of proinflammatory cytokines in tissue macrophages. Plasma CRP leveles were seen mildly increased the day after prolonged exercise[103].

TLRs. Limited evidence (confined to *in vitro* and murine models) points to a downregulation of Toll-like-receptors (TLR) with acute exercise[104]. TLRs are transmembrane proteins that detect microbial pathogens and they are involved in the recognition of endotoxins, like heat shock protein (hsp)[105]. Activation of TLRs results in a proinflammatory signalling cascades that have been associated with sedentary lifestyle ad systemic inflammation[106]. However, the physiological explanation behind the exercise-induced decrease in TLR expression remains to be clearly established.

Heat shock proteins. Exercise may also exert an anti-inflammatory effect by inducing the espression of 70-kDa family of heat shock protein (hsp70)[107]. In turn, the hsp70 initiation has been reported to suppress the proinflammatory activation of the nuclear transcription factor of κB family (NF-κB)[108]. NF-κB was shown as the first redox-sensitive eukaryotic transcription factor able to respond directly to oxidative stress in many cell types[109,110]. Basically NF-κB amplifies immune- and inflammatory responses in all cells. Hsp pathways have been also correlated with the modulation of peripheral autoimmunity[111].

Regulatory T cells. Exercise training was found to mobilize regulatory T cells (T_{reg}), which suppress immune responses[112]. In fact, T_{reg} cells are a considerable source of the anti-inflammatory cytokine IL-10[113]. Moreover, depletion of $CD4^+CD25^+$ T_{reg} can lead to autommunity and enhances immune response to foreign antigens[114,115].

Table I. Studies examining the effects of exercise interventions on inflammation and immunometabolism.

Authors	Design and target	Type of exercise	Main outcomes
Kadoglou et al[121]	Humans, diabetes	30-45 min AE 4 times/wk @ 50-75% VO_{2peak}, 6 mo	↓CRP, ↓IL-18, ↑IL-10
Nicklas et al[122]	Humans, elderly	150 min/wk walking, 12 mo	↓IL-6
Walther et al[123]	Humans, coronary heart disease	20 min daily AE @ 70% HRmax rate + 1 d/wk 60 min group aerobic session	↓CRP, ↓IL-6
Noble et al[124]	Humans, mice. Diabetes, energy metabolism	AE, high intensity exercise	↓ rates of obesity and T2D in mice; ↑ neuroplasicity and metabolism in humans
Gwffken et al[125]	Humans, elderly. Inflammation	Self-reported PA levels	↓CRP, ↓fibrinogen, ↓white blood cells, ↓Factor VIII activity
Fisher et al[126]	Humans, healthy	Endurance training	↓IL-6mRNA
Wang et al[112]	Mice, inflammation	Regular moderate-intensity exercise or prolonged, exhaustive high-intensity exercise	↓regulatory T cells
Lancaster et al[127]	Humans, healthy. Inflammation	Acute strenous exercise in the heat	↓TLR expression on circulating monocytes
Stewart et al[104]	Humans, healthy. Age, physical activity	12-week training program	↓$CD14^{+}$TLR expression (2,4)
Gleeson et al[128]	Humans, illness-prone athletes	endurance-based physical activity during the winter months	↑IL-10, ↑salivary IgA
Herbst et al[129]	Humans, children and adolescents with T1D	Self-reported regular physical activity	↓total cholesterol, ↓low-density lipoprotein cholesterol, ↓triglyceride levels
Huber et al[130]	Humans, children and adolescents with T1D	Two training sessions (lasting 90-120 min) per d (soccer, biking, hiking, swimming, ball games)	↓mean insulin dosage, ↓mean HbA1c, ↓total ghrelin levels
Phillips et al[131]	Humans, elderly	RE vs control, 3 d/wk for 10 wk	↓IL-6, ↓TNF-α
Balducci et al[117]	Humans, T2D and metabolic syndrome	RE + AE vs AE vs control (2 d/wk for 52 wk)	↑AD, ↓LP, ↓CRP, ↓IL-6, ↓TNF-α, ↑IS
Cuff et al[132]	Humans, obesity and T2D	RE + AE vs AE vs control (3 d/wk for 16 wk)	↓VAT, ↓SAT, ↑IS
Janssen et al[133]	Humans, obesity (women)	RE + CR vs AE + CR vs CR (3 d/wk for 16 wk)	↓VAT, ↓SAT, ↓fasting insulin, ↓insulin AUC
Rice et al[134]	Humans, obesity (men)	RE + CR vs AE + CR vs CR (3 d/wk for 16 wk)	↓VAT, ↓SAT, ↓fasting insulin, ↓insulin AUC
Atalay et al[107]	Rats, diabetes	Endurance training, 5 d/wk for 8 wk	↑hsp70 (↑ more pronounced in diabetic rats vs control)
Riechman et al[135]	Humans, healthy. Muscular physiology	RE, 3 d/wk @ 75% 1RM, for 10 wk	↑IL-15 after acute RE, but not chronically
Nielsen et al[136]	Humans, healthy, physically active subjects. Muscular physiology	RE acute protocol	↑IL-15mRNA
Ostrowski et al[93]	Humans, inflammation	Strenuos exercise (marathon)	↑IL-1ra, ↑TNF-α, ↑IL-10, ↑IL-6, ↑IL-1β

Abbreviations: ↑ = significant increase; ↓ = significant decrease; AE = aerobic exercise AD = adiponectin; BDNF = brain-derived neurotrophic factor; CR = caloric restriction; d = day; HR = heart rate; hsp = heat shock protein; IgA = immunoglobulin A; IL = interleukin; IS = insulin sensitivity; min = minutes; mo = month; LP = leptin; ns = not significant; PA = physical activity; RE = resistance exercise; 1RM = repetition maximum; T1D = type 1 diabetes; T2D = type 2 diabetes; TLR = toll-like receptors; TNF = tumor necrosis factor; VO_2 = oxygen uptake; wk = week; VAT = visceral adipose tissue; SAT = subcutaneous adipose tissue.

Limitations. *In vitro* measures have been extensively used to model the complex situation in humans, and only peripheral blood measurements have been performed in the majority of human studies investigating immunological responses to exercise[113]. Although determinant to mimic *in vivo* settings, animal studies are inconclusive to describe univocal inflammatory patterns. Non-obese diabetic (NOD) mice, as the elected experimental model analogous to human type 1 diabetes, can exemplify that dilemma[116]. High-intensity exercise training in a mouse running model resulted to increase expression of circulating T_{reg} cells more than a moderate-intensity regime, implying an augmented anti-inflammatory effect with an higher-intensity training[112]. This notion is supported by other studies and wonders on the suited volume of exercise to maximize beneficial health effects[117,118].

Consistent data from observational studies showing a link between self-reported levels of physical activity and inflammatory- or autoimmune biomarkers, as well as some promising data from randomized controlled trials[119], indicate that increasing aerobic activity could be effective for reducing chronic inflammation and insulin requirements in different dysmetabolic patients (Table I). However, the magnitude of the effects of physical activity on inflammatory mediators, and the amount of exercise necessary to produce clinically meaningful reductions in inflammations, has to be properly addressed. In this perspective, further human trials are warranted in order to tailor the optimal training regimes.

Integrative View and Concluding Remarks

Cytokines are involved in mediating the beneficial health effects of exercise in a crosstalk with organs and tissues (Figure 2), and they therefore play pivotal role in the protection against several diseases associated with systemic low-grade inflammation (Figure 1). This latter results in turn correlated to a broad immuno-metabolic scenario. It is nowadays clear that marked immune aberrancies are linked to several metabolic diseases. Thus exercise emerges as a cornerstone in the prevention, cure and treatment of all-species metabolic disturbances. In the view of novel pharamacological therapies targeted at different key organ/tissues, it is anyway harsh to conceive one universal drug capable of combatting all the diverse root causes. Intense efforts have been even made to discover active compunds that mimic or potentiate the effects of exercise training – the most notably "exercise mimetics". Nonetheless, it will be very improbable that one pill can reproduce the multiple health-promoting benefits rising from contracting muscles. In fact, researchers have even advocated the "polypill"[120] concept for the role of exercise, alluding to such wide-ranging positive perturbations on cells, tissues and organs.

The ultimate consideration of exercise as a *panacea* would be utterly esthetic if we just encourage people to do more, to be more phsycally active in a pandemic context of environmental syndromic factors.

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Conflict of Interest

No potential conflicts of interest relevant to this article were reported.

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