Type and Intensity as Key Variable of Exercise in Metainflammation Diseases: A Review

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ABSTRACT

Monocyte and lymphocyte subpopulations exhibit functions that vary between the anti- and pro-inflammatory spectrum, such as classic CD16- and non-classical CD16 + monocytes, as well as T helper 2 lymphocytes (Th2), the Th1/Th17 lymphocytes ratio, and T regulatory lymphocytes (Treg). Metabolic disease-associated inflammation is accompanied by an imbalance in monocyte and lymphocyte phenotypes and functionality, as well as a stronger proportion of inflammatory subpopulations. These changes appear to be important for the development and progression of diseases like diabetes and cardiovascular disease. On the other hand, the regular practice of physical exercise is an important tool to restore the functionality of monocytes and lymphocytes, and to balance the subtypes ratio. However, key variables regarding exercise prescription, such as the type of exercise, intensity, and volume differentially impact on the acute and chronic immune response in individuals diagnosed with meta-inflammation diseases. Here, we discuss the impact of different physical exercise protocols, acutely and chronically, on monocytes and lymphocytes of individuals with metabolic disease-associated inflammation. In this review, we focus on the best effects of different exercise protocols to dose the "exercise pill" in different inflammatory status.

Introduction

For decades it has been argued that obesity and physical inactivity are public, economic and clinical health problems [1]. The prevalence of obesity and physical inactivity has increased significantly worldwide [2], so that approximately half of the world's population is obese and physically inactive [3]. In this scenario, a sedentary lifestyle, overnutrition, and an unhealthy diet are risk factors interrelated with several metabolic diseases, such as obesity, type 2 diabetes *mellitus* (T2DM) [4], dyslipidemia [5] and non-alcoholic liver disease [6]. From an economic and public health perspective, if around 10 % of the world population became physically active, it

would prevent around half a million deaths annually and save billions of dollars annually in health care expenses [2]. Thus, it is necessary to identify strategies and target mechanisms involved in metabolic disease-associated inflammation [1]. Therefore, the mechanisms that support metabolic abnormalities is crucial in this perspective review.

Sophisticated studies have shown that the excessive intake of nutrients, especially saturated fatty acids and glucose, results in metabolic impairment, compromising not only organs and tissues but also the functionality of immune cells and, consequently, upregulation of classical inflammatory pathways [7–9]. The perpetuation of this systemic and local inflammatory environment, marked by the hyperactivation of immune cells and release of pro-inflammatory cytokines, favors insulin resistance, glucose intolerance, and accumulation of ectopic fat [10–12]. Together, these characteristics are associated with an increase in inflammatory monocytes and lymphocytes in the bloodstream, as well as a higher proportion of pro-inflammatory macrophages (M1) in metabolically active peripheral tissues, mainly adipose, hepatic, and skeletal muscle tissue [13–19]. In order to mitigate this inflammatory scenario, the physical exercise is a non-pharmacological strategy to attenuate the metabolic and inflammatory disturbance.

The practice of regular physical exercise is well-known as a promising strategy to restore the anti-inflammatory profile and reestablish the concentrations and store of energetic substrates, favoring the increase in T regulatory lymphocytes (Tregs), CD16-monocytes, and anti-inflammatory macrophages (M2), and enhancing insulin sensitivity and reducing body fat [13, 20–22]. Although physical exercise induces these changes, which may prevent or even reduce the deleterious effects, of metabolic disease-associated inflammation, previous studies have indicated that the type and intensity of physical exercise may be a key variable to optimize the subpopulations and function of immune cells [23, 24]. Thus, knowledge about the alterations caused by intensity or type of exercise in monocytes and lymphocytes in individuals with metabolic diseases could favor the development of more appropriate treatment or prevention strategies. Therefore, the two main purposes of this perspective review are 1) to highlight the intensity and type of exercise, both acute and chronic, as key variables to provoke morphofunctional changes in monocytes and lymphocytes in metabolic disease-associated inflammation and 2) to elucidate the mechanisms proposed to be involved in the regulation of metabolic disease-associated inflammation induced by physical exercise.

Type of exercise and intensity as key variable on monocytes and lymphocytes morpho-functional changes: Does it really matter?

Over the past few years, several studies have extensively investigated the effects of physical exercise and physical fitness status on changes in immune cells in different scenarios (health, metabolic diseases, and aging). The practice of different types of exercise – i.e., aerobic and strength exercise, different intensities, volumes, and schemes, has been the central discussion in guidelines to promote global improvement in health, such as musculoskeletal, neu-

ro-endocrine-metabolic, and cardiovascular adaptations in individuals with metabolic diseases [25, 26]. However, a consensus on the effect of different exercise protocols – acutely and chronically, on systemic anti-inflammatory adaptations in individuals with metabolic diseases remains limited.

Acute exercise session and metainflammation diseases

It is well described that a single session of physical exercise induces changes in inflammatory markers, regardless of changes in body fat [27–29]. In addition, the changes found after an acute physical exercise session may support the understanding of long-term adaptations [30–32]. The literature includes few studies on the influence of a single session of physical exercise on the population of lymphocytes and monocytes (▶ **Table 1**). We will highlight the main findings of the studies found below.

Obesity, overweight and sedentary behavior

The response of monocytes, lymphocytes, or peripheral blood mononuclear cells (PBMCs) in obese patients has been evaluated predominantly by aerobic exercise sessions, performed in different schemes and intensities, such as continuous and moderate- intensity [33], continuous and high volume (marathons) [34], high-intensity intermittent exercise (HIIE) [21, 35, 36] and higher efforts (to exhaustion) [37–39]. Slusher et al. [33] applied a 30-minute session of continuous aerobic exercise at 75 % of peak oxygen consumption ($\dot{V}O_{2peak}$) in obese and eutrophic individuals. The authors demonstrated that the exercise session reduced the synthesis of interleukins- 6 and 10 (IL-6 and IL-10) and pentraxin-related protein (PTX-3) in lipopolysaccharides (LPS)-stimulated PBMCs in both groups, but the synthesis of tumor necrosis factor- alpha (TNF-α) remained unchanged. From a clinical point of view, these findings may be considered negative for obese individuals, since they already present less synthesis of IL-10 in LPS-stimulated PBMCs at rest. However, due to the similar response to the eutrophic group after physical exercise, this suggests a balanced response of PBMCs to the inflammatory stimulus, endorsing the need for further studies with a continuous aerobic session of moderate intensity. Additionally, continuous aerobic exercise with high volumes, such as the marathon, led to reduced expression of toll-like receptor (TLR-4) gene in obese and lean individuals immediately after the race. Still, 24-h after the race an increase in gene expression was observed, as well as a decrease in the protein content [34]. Due to the strenuous nature of the marathon, the inflammatory potential was reflected by the systemic increase in IL-6, IL-10, and TNF-α, however, the concentrations of TNF-α and C-reactive protein remained high after 24-h. Furthermore, the monocytosis observed during acute exercise is frequently associated with increases in monocyte chemoattractant protein type-1 (MCP1) and other chemotactic factors, suggesting monocyte migration to inflamed tissue (i. e. muscle tissue) during the bout [34].

On the other hand, HIIE is used as an alternative strategy to achieve similar adaptations from traditional moderate aerobic exercise [40]. Compared to exhaustive physical exercise (stepping up and down from a step), 10 bouts of 60 s (at 85–90 % maximal aerobic velocity (MAV)) differentially altered the subpopulations of CD4$^+$ T cells in obese individuals, increasing the proportion of cells

▲ **Table 1** Effects of acute exercise on the phenotype and function of systemic monocytes and lymphocytes in humans with chronic inflammatory diseases.

Design	Exercise protocol	Results	Other information
Obesity, overweight and/or sedentary			
Huang et al. (2019) [38] 2 groups (M) ▪ Obese group (OB) (n=6, 27.7y) ▪ normal-weight healthy group (NW) (n=6, 24.8y)	▪ Maximal graded exercise test on a treadmill. ▪ The maximum exercise protocol started with a 3-minute warm-up at 60% of HRmax predicated by age, followed by an increase in speed up to 80% of HRmax. Subsequently, the grade was increased by 2% every two minutes until exhaustion.	▪ Before exercise (basal), PBMCs: lower Bcl-2 protein expression in the OB compared to NW. There were no differences in LC3-I and LC3-II protein expression or the LC3-II/LC3-I ratio between groups. ▪ Immediately after exercise: lower Bax and higher Bcl-2 protein expression in the OB compared to NW. Higher LC3-II/LC3-I ratio and LC3-II/LC3-I AUCi in the OB compared to NW.	▪ Before exercise (basal): Bcl-2 protein expression was negatively correlated with BMI, HOMA-IR, and fasting insulin blood concentration. ▪ Immediately after exercise: Bax/Bcl-2 AUCi was negatively correlated with BMI, and waist and hip circumferences. LC3-II/LC3-I AUCi was positively correlated with BMI, waist and hip circumferences, and fasting insulin blood concentrations.
Slusher et al. (2017) [33] 2 groups (18 to 35y) ▪ Sedentary obese group (OG) (n=10, 4M+6F, 23.3y). ▪ normal-weight healthy group (NWG) (n=11, 5M+6F, 23y).	▪ 30min of continuous exercise at 75% VO_{2peak} on a treadmill.	▪ Before exercise (basal), PBMCs: lower LPS-stimulated IL-10 production in the OG compared to NWG. There were no differences in LPS-stimulated PTX3, IL-6, and TNF-α production. ▪ Immediately after exercise: Decrease in LPS-stimulated IL-10, IL6, and PTX-3 production, but not TNF-α, in both groups.	▪ Before exercise (basal): higher VO_{2peak} in NWG compared to OG.
Peres et al. (2020) [39] 4 groups (M, 18 to 30) ▪ sedentary lean group (SL) (n=10, 25.8y). ▪ regular exercisers lean group (EL) (n=10, 26.5y). ▪ sedentary obese group (SO) (n=10, 24.5y). ▪ regular exercised obese group (EO) (n=10, 25.9y).	▪ Cardiopulmonary exercise testing was individually increased for each participant considering their physical condition and treadmill tolerance using a ramp protocol. The load was individually increased for each participant considering their physical condition and tolerance. ▪	▪ After exercise: increase in monocyte and lymphocyte counts in both groups immediately after exercise, remained higher 1-h after bout, except for SO (number of lymphocytes below baseline after 1-h). ▪ Decrease in DNA damage in PBMC non-stimulated concomitant with an increase in GSH content immediately after exercise in all groups, followed by increases in DNA damage and TBARS levels 1-h after the exercise in EO and SO. ▪ Higher DNA damage index and TBARS levels immediately after exercise in PBMCs (stimulate with H_2O_2 25 μM and 50 μM) in all groups, remaining higher in SL, SO, and EO. ▪ PBMC from SO collected 1-h after exercise and exposed to H2O2 presented the highest DNA damage and lower GSH content compared to the other groups.	▪ Before exercise (basal): higher glucose blood concentration in the SO compared with other groups and higher TG blood concentration compared with EO. Higher HDL-c blood concentration in the EL compared with other groups and lower CRP blood concentration compared with EO.
Dorneles et al. (2019) [21] 2 groups (M) ▪ Sedentary group (SG) (n=15, 26.1y). ▪ Physically active group (AG) (n=15, 25.3y).	▪ HIIE: 10 bouts of 60s (85–90% MAV) alternated with 75s of recovery (50% MAV) on a motorized treadmill.	▪ Before exercise (basal): Higher mTeff (CD4+CD25−CD39+) and lower mTreg (CD4+CD25+CD39+) proportions in the SG compared to AG. Higher expression of CD39 on CD4+CD25+ cells of AG compared to SG. ▪ After exercise: Increase in CD4+, CD4+CD25+ and CD4+CD25+CD73+ T cell frequency immediately after the HIIE followed by a decrease to below baseline in the AG 1-h after HIIE. ▪ Increase in mTreg and mTeff frequency immediately after the HIIE in both groups. Decrease in mTeff to below baseline in the AG 1-h after HIIE. ▪ Increase in CD39 expression on CD4+CD25− and CD4+CD25+ T cells immediately after HIIE in both groups, remaining higher 1-h after HIIE except for CD4+CD25− T cells in the AG. ▪ Higher CD39 expression on CD4+CD25+ T cells in AG compared with SG immediately after and 1-h after HIIE.	▪ Before exercise (basal): higher VO_{2peak} in the AG compared to SG. ▪ VO_{peak} values positively correlated with the baseline frequencies of mTreg cells (CD4+CD25+CD39+) and negatively correlated with the mTeff cells (CD4+CD25−CD39+).

▲ **Table 1** Continued.

Design	Exercise protocol	Results	Other information
Nickel et al. (2012) [80] 3 groups (M, 30 to 60y) ■ Obese amateur marathon runners (ONE) (n = 15, 40y) ■ Lean non-elite (LNE) (n = 16, 40y) ■ Lean elite (LE) (n = 16, 40y)	■ Marathon	■ After marathon, PBMCs: There were changes in the TLR-2 gene and protein expression between groups. ■ Decrease in TLR-4 gene expression in the LNE immediately after, which was not reflected in the protein-expression. After 24-h, up regulation of the mRNA expression was seen in all groups compared to baseline. ■ Decrease in TLR-4 gene expression for all groups immediately after, and increase compared to baseline 24-h after. Decrease in protein expression only 24-h after marathon for all groups.	■ Before marathon (basal): Lower IL-6 blood concentration in the LE compared to LNE and ONE (principally). Lower IL-10 blood concentration in the ONE compared to LNE and LE. ■ After marathon: Increase in IL-6 blood concentration immediately after and decrease without yet reaching baseline levels after 24-h for all groups. ■ Increase in IL-10 blood concentration immediately after and decrease to baseline values after 24-h for all groups. ■ Increase in TNF-α blood concentration after 24-h for all groups. ■ Increase in PCR blood concentration after 24-h for all groups.
Phillips et al. (2008) [45] 4 groups (W, 64 to 72y) ■ Non-hormone replacement (NHR = 9) ■ Selective estrogen receptor modulator (SER = 7) ■ Resting control (non-hormone replacement, CON = 7)	■ NHR, HRT, and SER exercised (3 sets, 10 exercises, 80 % 1RM) ■	■ Resistive exercise increased post exercise serum IL-6, and post exercise LPS-stimulated IL-6 and IL-1 beta. ■ LPS-stimulated IL-1 beta remained elevated after 2-h in exercised group and was significantly higher than pre-exercise in CON after 2-h. ■ Expressed per monocyte, exercised group had significantly lower IL-1 beta and TNF-alpha LPS-stimulated production at post exercise and after 2-h compared to CON, indicating an exercise-induced blunting of an apparent diurnal response on cytokine production.	
Bay et al. (2020) [51] 5 groups (M and F, above 18y) ■ no exercise + placebo ■ no exercise + tocilizumab ■ exercise + placebo ■ exercise + tocilizumab ■ (5) resistance training + placebo as parallel groups.	■ The acute exercise bout consisted of the following: 4 min warm- up at 40 % of $\dot{V}O_{2max}$, another 4 min warm-up at 60 % of $\dot{V}O_{2max}$, then 3 × 2 min work-outs at 75 % of $\dot{V}O_{2max}$ with 1 min recovery at 30 % between the 2 min work-outs, 8 min at 40 % of $\dot{V}O_{2max}$, a second set of 3 × 2 min intervals at 75 % of $\dot{V}O_{2max}$ with 1 min recovery at 30 % between the 2 min work- out, and finally 10 min of cool down at 50 % of $\dot{V}O_{2max}$.	■ IL-6 receptor blockade attenuated the increase in NK cells by 53 % ■ Dendritic cells increased by 66 % induced by an acute bout of exercises. ■ No changes were observed for T cells, monocytes, and neutrophils.	■ Adrenaline response before and after saline infusion showed a slightly delayed response, which resulted in lower adrenaline levels 22 min into the exercise bout. ■ Noradrenaline responses to the acute exercise bout were similar before and after infusion of saline.

Design	Exercise protocol	Results	Other information
Dorneles et al. (2020) [35] 2 groups (M, 24 to 32y) ▪ Sedentary normoglycemic obese (n = 8)	▪ The HIIE session consisted of a warm-up (5 min) at a workload eliciting 40 % HRmax. The HIIE consisted of 10 bouts of 60 s (85–90 % MAV) alternated with 75 s of recovery (50 % MAV) on a motor-ized treadmill. ▪ The exhaustive exercise consisted of stepping up and down from a step adjusted to the height of each subject's femoral condyles9,81. The stepping rhythm was paced acoustically at 60 beats per min with the same periods (1 s) for stepping up and down, respec-tively.	▪ In vitro experiments revealed that post-HIIE serum reduced the histone H4 acetylation status and NF-κB content of ▪ Production suppressed of both TNF-α and IL-6 by PBMCs, while increasing IL-10 production. ▪ Post-exhaustive exercise serum induced histone H4 hyperacetylation and mitochondrial depolarization in lymphocytes and increased TNF-α production. ▪ In vitro post-HIIE serum incubation resulted in an increase in the frequencies of CD4 + CTLA-4 + and CD4 + CD25 + T cells expressing CD39 and CD73. ▪ Post-exhaustive exercise serum decreased the frequency of CD4 + CD25 + CD73 + T cells but increased CD4 + CD25–CD39 + T cell frequency. ▪ Both post-exercise serums increased the proportions of CD4 + PD-1 + and CD8 + PD-1 + T cells.	▪ Exhaustive exercise revealed higher TBARS production compared to HIIT ▪ ROS production was higher after exhaustive exercise compared to HIIT.
T2DM or insulin resistant			
Durrer et al. (2017) [14] 2 groups (no gender distribution reported). ▪ T2DM patients' group (2TDM) (n = 10, 57.9y). ▪ Healthy age-matched controls group (CG) (n = 9, 55.8y).	▪ Session of HIIE. ▪ 2TD and CG: 7 × 1-min intervals at 85 % PPO with 1-min rest periods at 15 % PPO.	▪ After exercise: increase in total leukocytes count immediately after in both groups and decrease to baseline values after 1-h. Higher leukocytes count in the T2DM compared to CG. ▪ Increase in lymphocytes, classical, and CD16 + monocytes immediately post-exercise in both groups. ▪ Decrease in TLR-2 expression on classical and CD16 + monocytes immediately and 1-h post-exercise in both groups. ▪ Higher TLR-4 expression on CD16 + monocytes in the 2TD compared to CG across all time points.	▪ Before exercise (basal): Higher VO$_{2peak}$ in the CG compared to 2TDM. ▪ After exercise: Decrease of TNF-α blood concentration 1-h after exercise in both groups, however, CG showed a greater reduction. ▪ Decrease in LPS-stimulated TNF-α production in the whole blood 1-h after compared with pre and immediately after exercise in both groups. When corrected for total leukocyte numbers, T2DM released less TNF-α than CG.
McCormick et al. (2019) [58] 2 groups (27 to 61 y) ▪ Prediabetic group (PD) (n = 6, 3 M + 3 F, 44.4y). ▪ Age and sex matched control group (CG) (n = 6, 3 M + 3 F, 42.4y).	▪ Aerobic exercise session on the bike. ▪ 50 % of VO$_{2peak}$ for 60 min with 5 min of rest interspersed every 20 min.	▪ Before exercise (basal), PBMCs: Increase in LC3-II protein content after baflomycin treatment in the CG, but not PD. ▪ Increase in LC3-II protein content after rapamycin treatment in both groups, however, increase in the CG was higher than the PD. ▪ Increase in LC3-II/LC3-I ratio after baflomycin + rapamycin treatment for CG, but not PD. ▪ Lower MAP1LC3B and p62/SQSTM1 gene expression in the PD compared to CG under all conditions. ▪ After exercise: Increase in LC3-II protein content after 4-h in the CG. Decrease in LC3-II/LC3-I ratio immediately after exercise and restored after 4-h in the CG.	▪ Before exercise (basal): There were no differences in % body fat and VO$_{2peak}$ between groups.

▲ **Table 1** Continued.

Design	Exercise protocol	Results	Other information
De Matos et al. (2016) [59] 3 groups (18 to 55 y) ▪ Lean insulin sensitive group (LIS) (n = 8, 3 M + 5 F, 37 y). ▪ Obese insulin sensitive group (OIS) (n = 9, 3 M + 6 F, 38 y). ▪ Obese insulin resistant group (OIR) (n = 8, 3 M + 5 F, 40 y).	▪ 60 min. of cycling at 60 % of the VO_{2peak} with passive rest every 20 minutes	▪ Before exercise (basal): Higher % of CD16+ monocytes and monocyte count in the OIR compared to LIS, but no differences between LIS and OIS. There was no difference in the % of CD16- monocytes between groups. ▪ Positive correlation between the % of CD16+ monocytes and BMI, waist circumference, HOMA1-IR, insulin, TC, VLDL-c, and TG blood concentration. Negative correlation between the % of CD16- monocytes and TG. ▪ After exercise: Increase in the number of total leukocytes, lymphocytes, and monocytes. Decrease in the % of CD16+ monocytes in all the groups. There was no difference in the % of CD16- monocytes.	▪ Before exercise (basal): There were no differences for VO_{2peak}, and HDL-c, LDL-c, and glucose blood concentrations between groups. ▪ Higher HOMA1-IR and TG, VLDL, and insulin blood concentrations in the OIR compared to LIS and OIS. Higher TC in OIR compared to LIS. Higher HOMA1-IR in obese (OIS and OIR) compared to LIS.
MetS			
Wonner et al. (2018) [64] 3 groups ▪ Healthy control group (CG) (n = 10, 4 M + 6 F, 34 y). ▪ Risk of MetS group (RM) (n = 7, 3 M + 4 F, 48 y). ▪ MetS Group (MG) (n = 6, 4 M + 2 F, 43 y).	60 sec or until exhaustion of cycling at 400 W	▪ Before exercise (basal): Lower CD14+ CD16-/CD14+ CD16+ ratio in the MG. ▪ After exercise: Increase in monocyte subpopulations, and monocyte, lymphocyte, and leukocyte count in both groups. ▪ Increase in % of CD14+ CD16+ and CD14-CD16+ monocytes in both groups. Smallest increase in CD14-CD16+ + monocyte count in the MG. ▪ Decrease in CD14+ CD16-/CD14+ CD16+ ratio in both groups after exercise.	▪ Before exercise (basal): Higher BMI, weight, and glucose blood concentration in the MG compared to RM and CG, and RM compared to CG. Lower HDL-c blood concentration in the MG compared to RM and CG, and RM compared to CG. ▪ After exercise: Increase in HDL-c2/3, C4, and decrease in C3c blood concentration in the CG. Decrease in LDL-c, HDL-c, HDL-c3, and C3c and increase in C4 in the RM. There were no changes in the MG.

Note: MAV: maximum aerobic velocity, HIIE: high-intensity intermittent exercise, HRmax: heart rate maximum, VO_{2peak}: peak oxygen consumption, RM: maximum repetition, CD: cluster differentiation, TBARS: thiobarbituric acid reactive substance, IGF-1: insulin-like growth factor-1, NF-κB: nuclear factor kappa B, H4Ac: histone H4 acetylation, LC3: light chain 3, Bax: B-cell lymphoma 2-associated X protein, Bcl-2: B-cell lymphoma 2, HOMA1-IR: homeostatic model assessment 1 of insulin resistance, PTX3: pentraxin 3, H2O2: hydrogen peroxide, GSH: glutathione, CRP: C-reactive protein, ROS: reactive oxygen species, CTLA-4: cytotoxic T lymphocyte antigen-4, SVC: stroma-vascular cell, MAP1LC3B: microtubule-associated protein 1 light chain 3 beta, p62/SQSTM1: sequestosome-1, ADA: adenosine deaminase, E-NTPDase: ectonucleoside triphosphate diphosphohydrolase, ALT/AST: alanine aminotransferase/aspartate aminotransferase ratio, IL-: interleukin, TNF-α: tumor necrosis factor-alpha.

expressing anti-inflammatory markers [35]. In addition, PBMCs incubated with the serum collected after the HIIE session showed less expression of transcription nuclear factor- kappa B (NF-κB) and histone H4 acetylation, reduced synthesis of IL-6 and TNF-α, and increased synthesis of IL-10 [35]. Unlike, PBMCs incubated with serum collected after an exhaustive session showed greater release of TNF-α, histone H4 acetylation expression, and membrane depolarization [35]. These results were accompanied by a higher anti-inflammatory systemic profile after the HIIE session compared to the exhaustive session [35].

In addition, similar responses were found in overweight-obese or sedentary individuals after the same HIIE protocol (10 bouts of 60 s (at 85–90 % MAV)), with an increase in the histone deacetylase 2 activity in PBMCs, accompanied by an increase in IL-10, transforming growth factor-beta (TGF-β), and IL-6 blood concentrations [36] or an improvement in the proportion of memory Treg cells (mTreg) and a decrease in memory T effector cells (mTeff), as well as an increase in CD39 expression, and CD73 on the surface of CD4+T cells [24], respectively. CD39 and CD73 are ectonucleotidases responsible for the metabolism of adenosine triphosphate (ATP) into intracellular adenosine, contributing to the immunosuppressive function of Treg cells and reducing the production of inflammatory cytokines and chemokines [41–43]. Therefore, HIIE protocols appears to be a good strategy for reducing pro-inflammatory signaling in PBMCs, as well as regulating the T cell subpopulations. Furthermore, Gustafson and coworkers [44] identified a positive correlation Treg mobilization during endurance exercise and % body fat, suggesting greater benefits of exercise to induce immunoregulatory properties, as well as the participation of adipose tissue in lymphoid cell mobilization.

Research has been conducted on possible changes in oxidative stress and apoptosis after a maximum aerobic exercise session. After a maximum progressive aerobic test (maximum test) on the treadmill, the PBMCs of obese individuals showed higher protein expression of anti-apoptotic Bcl-2 and the LC3-II/LC3-I ratio, and lower protein expression of pro-apoptotic Bax compared with eutrophic individuals. Interestingly, the same study showed that after exercise the Bax/Bcl-2 ratio was negatively correlated with the body mass index (BMI) and waist and hip circumferences, and the LC3-II/LC3-I ratio was positively correlated with BMI, waist and hip circumferences, and fasting insulin blood concentrations [38]. These findings suggest that the PBMCs of obese individuals exhibit a greater increase in autophagic flow and less apoptosis after the maximum exercise compared to eutrophic individuals, possibly through a regulatory mechanism for survival in the inflammatory environment [38]. On the other hand, after maximum test on the treadmill, there was a reduction in DNA damage and increase in the content of intracellular total glutathione (GSH) in unstimulated PBMCs from trained and sedentary obese individuals and only lean sedentary individuals. However, after 1-h there was an increase of DNA damage and thiobarbituric acid reactive species (TBARS) production only in obese individuals [39]. Additionally, the PBMCs of sedentary obese individuals stimulated with hydrogen peroxide (H_2O_2) showed greater DNA damage and less total GSH compared with sedentary eutrophic subjects and trained obese subjects after the maximum exercise session [39]. The exhaustive exercise also increased the inflammatory monocytes percentage, histone H4

acetylation and reduced the histone deacetylase 2 activity in obese individuals [37]. The same study showed an increase in the inflammatory cytokines' secretion in PBMC and an increase in systemic markers of oxidative damage after exhaustive exercise. Together, these findings show the requirement for caution in the maximum exercise prescription when aiming at anti-inflammatory and antioxidant effects in the obese population.

On the other hand, the effects of an acute session of strength exercise on immune cells in obese individuals are still not well characterized. In post-menopausal obese women, resistance exercise sessions (3 sets x 80 % 1RM, 10 exercises) blunted the LPS-stimulated IL-1β and TNF-α production by whole blood cells [45], suggesting downregulation of TLR-4 in innate immune cells linked to inflammatory response. In lean volunteers, monocytosis was observed immediately after a single session of resistance training consisting in 4 sets of leg press, knee extensor and leg curl at 65 % of 1-RM [46]. Interestingly, monocytes recruited after strength exercise sessions had a nonclassical phenotype, characterized by higher CD16 + expression, proinflammatory functions and express higher levels chemokine receptors and integrin molecules on the cell surface which indicates their migratory capacity [47, 48]. However, resistance exercise had little impact on Treg and CD8 + T cell mobilization compared to endurance exercise, suggesting that physiological differences between exercise types may alter the acute immune response [49]. The same group identified superior effects of endurance exercise to activate the axis of programed cell death protein 1 (PD-1)/aryl hydrocarbon receptor signaling in CD8 + T cells, important signaling to cell survival a function, compared to resistance exercise in healthy males [50]. Given the importance of strength-based exercise in the treatment of obesity, future studies should be conducted to evaluate the acute effects of strength exercise or combined strength plus endurance exercise sessions on monocyte and T-cell mobilization in obese individuals.

The immune cell mobilization during acute exercise seems to be mediated by the adrenergic response and systemic cytokine levels in obese individuals. During exercise, natural killer (NK) cells, myeloid cells (neutrophils, monocytes, and dendritic cells), and T and B cells are recruited from lymphoid and non-lymphoid organs to the peripheral circulation for an effective immune response against non-self-particles (i. e., pathogens and allergens) or danger-associated molecular patterns (DAMPS). In a cancer murine model, exercise-induced infiltration of NK cells in the tumors was dependent on IL-6 signaling. In this sense, a recent study demonstrated that IL-6 receptor blockade attenuated the mobilization of NK cells (− 53 %) and DC cells (− 66 %) of obese men induced by an endurance exercise bout, through abolishment of IL-6 receptor signaling [51]. Since IL-6 is one of the most recognized myokines, we postulate that exercise-induced myokine release from contracting skeletal muscle may impact immune cell mobilization during acute exercise. Furthermore, adrenergic response directly impacts on leukocytosis [52]. In healthy lean individuals, the preferential mobilization of NK cells, non-classical monocytes and central and effector memory CD8 + T-cells were largely dependent of catecholamine signaling through the β2-Adrenergic Receptor. However, there is a lack of evidence regarding catecholaminergic impact on immune cell mobilization of obese human individuals. In obese mice model, exercise modulates β2 adrenergic regulation of innate

function of monocytes, mainly the phagocytic activity, and induced an anti-inflammatory profile [53, 54]. In this sense, both adrenergic response and IL-6 may crosstalk during physiological stress conditions [55], and the acute release of both mediators may contribute to the anti-inflammatory phenotype of circulating immune cells during exercise. In fact, the incubation of resting mononuclear cells of obese men with plasma obtained immediately after HIIE elicited higher frequencies of CD4 + CD25 + T cells expressing CTLA-4, CD39, and CD73, suggesting a role of blood factors released during exercise to induce an immunoregulatory phenotype of CD4 + T cells [35]. Furthermore, high-fat diet-induced obese mice subjected to an acute bout of treadmill exercise presented increased signaling of IL-6 and immunoregulatory IL-10 concomitant to the proportion of F4/80 + CD11c + M1 macrophages in adipose tissue, suggesting a role of exercise-induced myokine release on immunoregulatory properties of immune cells [56]. However, acute endurance exercise did not change the immune cell population, including macrophages and T cells, of adipose tissue from obese men, despite the reduction in adipose tissue progenitor cells [57].

T2MD or insulin resistant

Glycemic control and inflammatory profile in T2DM are important variables modulated by the acute exercise session. Predominately light to moderate intensity in continuous aerobic exercise sessions [58, 59] and HIIE [14] has been investigated, however, no data regarding strength exercise were found in the literature search. Individuals with T2DM and healthy controls underwent an HIIE session characterized by 7 bouts of 1-min intervals at 85 % of peak power output (PPO) with 1-min rest periods at 15 % PPO [14]. Immediately after HIIE, there was an increase in the number of CD16$^+$ and classic monocytes and lymphocytes, as well as a reduction in the expression of TLR-2 over classic and CD16$^+$ monocytes in both groups after 1-h. Cellular changes were accompanied by reduced production of TNF-α stimulated with LPS in whole blood culture and blood circulating concentrations of TNF-α after 1-h. These findings suggest similar anti-inflammatory effects in individuals with or without T2DM after a HIIE session [14].

Of note, the increase in CD16$^+$ monocytes in individuals with T2DM after HIIE session was accompanied by a reduction in inflammatory response by decreasing in the TLR-2 expression [14]. However, a different anti-inflammatory response was found after 60 minutes of cycling at 60 % of $\dot{V}O_{2peak}$ [59]. Additionally, in the same study the total number of monocytes and lymphocytes increased, however, accompanied by a reduction in the percentage of CD16$^+$ monocytes of individuals with obesity and insulin resistance. Interestingly, the percentage of CD16$^+$ monocytes was positively correlated with BMI, waist circumference, HOMA1-IR, insulin, triacylglycerol, very low-density lipoprotein (VLDL-c) and total cholesterol [59]. Therefore, mobilization and anti-inflammatory responses on CD16$^+$ monocytes appear to be dependent on the modality and intensity of aerobic exercise, most likely due to adrenergic mechanisms and endothelial shear stress [52, 60]. In addition, acute exercise increases insulin-induced activation of AKT Thirosine308-phosphorylation in adipose tissue resident macrophages of HFD mice concomitant with increased SOCS3 and STAT3 phosphorylation, suggesting that changes acute increases in insulin sensitive in macrophages of obese men is linked to an anti-inflammatory phenotype [56]. In line with this, obese insulin resistant men presented increases in insulin-binding circulating monocytes after prolonged aerobic exercise [61]. Acute ameliorations of immunometabolic response of monocytes to exercise may help to decrease the hyperresponsiveness of innate cells to the action of immunoregulatory IL-10 concomitant to low action of binding of insulin in these cells [62].

Regarding autophagic capacity, 60 minutes of aerobic exercise at 50 % of $\dot{V}O_{2peak}$ was not enough to reverse the impaired autophagic flow of PBMCs of pre-diabetic subjects compared to healthy subjects [59]. The same study showed that treatment with rapamycin (pharmacological mTOR inhibitor) also did not reverse the imbalance in the autophagic flow in the prediabetic group, thus, despite mTOR being associated with inhibition of autophagy and possibly linked to the pro-inflammatory profile of PBMCs in patients with T2DM [63], it is possible that the very low intensity exercise session did not sufficiently stimulate the autophagic regulatory pathways.

MetS

Studies evaluating the effects of the acute exercise session on the response of monocytes and lymphocytes of individuals with MetS are still scarce in the literature. Despite the use of unconventional exercise protocol, Wonner et al. [64] verified the influence of a 60-second session or even exhaustion (fixed power of 400 W on cycle ergometer) on leukocytes of individuals with MetS, risk of MetS and healthy control group. After the session, there was an increase in the lymphocyte count and monocyte subpopulations in all groups, as well as an increase in the percentage of intermediate and non-classic monocytes. However, the study did not verify the morphofunctional characteristics of these cells. Moreover, the lipid profile was modulated in individuals at risk for MetS, with no change in the MetS group, suggesting an insufficient stimulus for lipid modulation in this group. It is important to mention that, due to the greater capacity of intermediate and non-classic monocytes to patrol the endothelium and potential adhesion in the endothelial wall (marginal reservoir), acute exercise preferentially modulates these cells into the bloodstream mediated by β2-adrenergic receptors [52]. Interestingly, it is suggested that this mechanism contributes to the protective effect on endothelial health [64]. Furthermore, in a mice model of MetS exercise alleviates insulin resistance through downregulation of TLR4-mediated ERK/AMPK signaling pathway in tissue resident macrophages, demonstrating that exercise may acutely change metabolic parameters through the reduction of inflamed innate cells [65].

Taken together, the scarcity of studies on the effects of an acute exercise session on the proportion and morphofunctional characteristics of monocytes and lymphocytes of individuals with metabolic diseases makes comparative analysis difficult. In summary, except for exhaustive aerobic protocols, a moderate-intensity continuous aerobic exercise session or HIIE seem to be good strategies to counteract the inflammatory environment. Thus, the greatest possible number of acute exercise sessions developed throughout the week (respecting the recovery period) could be an effective strategy to maximize gains from the transient anti-inflammatory effect of each exercise session. Therefore, in the next topic, we will elucidate the influence of the practice of physical exercise in the long term.

Chronic adaptations to the training period

Since systemic inflammation have a central role in metabolic diseases, such as MetS, obesity, NAFLD and T2DM, the modulation of monocytes, lymphocytes and PBMCs can be an important tool for anti-inflammatory effects. For example, the reduced release of TNF-α by PBMCs was associated with reduced glycemic responses and a lower circulating concentration of TNF-α after training period [66]. Additionally, the physical training is considered a good tool to reduce reactive oxygen species (ROS), fat content and inflammation in the liver, contributing to the treatment of diseases like NAFLD [67]. However, the type, intensity and volume of exercise are variables normally associated with the type of adaptation generated but with uncertain response regarding immune adaptations in metainflammation diseases.

Therefore, here we will discuss the influence of different chronic stimuli on monocytes, lymphocytes, and PBMCs of individuals with metabolic diseases, in order to describe possible similarities and differences in the adaptations provided (▶ **Tables 2** and ▶ **3**). The variety of possibilities may favor adherence to training and, consequently, contribute to disease treatment.

Obesity, overweight and sedentary behavior

From an immunological point of view, an increasing number of studies have been analyzing the influence of HIIT and MICT protocols on immune cells in obese and sedentary individuals [68–70]. In a training model designed to decrease changes in body fat. Barry et al. [68] engaged obese and sedentary individuals in the following protocol, 2 weeks (5 days a week) of HIIT or MICT. Individuals from HIIT group performed 4×1 min to 10×1 min intervals at 90% HRreserve with 1 minute of active recovery and individuals from MICT group performed 20 min to 50 min continuous up to ~65% HRmax. Despite similarities between the results, such as no differences in monocyte and lymphocyte counts and no reduction of classic monocytes expressing CXCR2, the HIIT protocol increased the percentage of classic monocytes, intermediate monocytes and T cells expressing CCR5, while MICT protocol decreased the percentage of intermediate monocytes positive for CCR2 and CXCR2 expression. The findings suggest that MICT protocol may reduce the monocyte migration (via reduced MCP-1 receptor) and HIIT protocol positively regulates monocyte and T cell migration (via increased MIP-1α receptor). Additionally, the same HIIT and MICT protocol was used by the same research group in order to verify the anti-inflammatory action of IL-10 and IL-6 in obese and sedentary individuals [69]. After the training period, there were no changes in the expression of the IL-6 and IL-10 receptor, count of classic monocytes and T cells and concentration of circulating cytokines (TNF-α, IL-6 and IL-10). However, in whole blood culture stimulated with LPS, both protocols reduced the anti-inflammatory action of IL-10 and IL-6, and HIIT group showed greater impact. Another study compared the effect of 10 weeks of HIIT (15 to 60 seconds of repeated sprints at 90% HRmax) or MICT (30 to 45 minutes at 70% HRmax) on the function of monocyte subpopulations in sedentary individuals [70]. Neither protocol changed the monocyte and lymphocyte count, but both increased phagocytosis of classic monocytes and the percentage of monocytes displaying oxidative burst, as well as reducing the percentage of intermediate monocytes and expression of TLR-2/4 in CD16⁺ monocytes. However, interesting-

ly, the HIIT but not the MICT reduced the percentage of non-classical monocytes. In addition, monocytes seem to be less activated after both moderate-intensity combined exercise training and short-term HIIT, as identified by lower HLA-DR expression on the monocyte cell surface, which suggests that exercise changes the inflammatory activation status of monocytes in obese individuals [22, 71]. Additionally, HIIT seems to favor epigenetic mechanisms that protect against oxidative stress [72], as well as the MICT increased the number of CD4⁺ and CD8⁺ T cells (with no change in the total number monocytes) after training period [73]. Taken together, HIIT and MICT protocols appear to promote immune modulations, such as reducing the population of CD16⁺ monocytes and the expression of TLR-2 and 4 in these cells, restoring the balance between monocyte subtypes and contributing to negative regulation inflammatory profile in obese individuals. On the other hand, compared to the adaptations induced by MICT, HIIT protocol seems to potentiate the innate response of monocytes against stress challenges, evidenced by increase in migration receptors and greater production of TNF-α after anti-inflammatory stimulus. These findings may be linked to the nature of high-intensity exercise, providing greater contact with inflammatory agents, like LPS [74]. The same is seen in obese marathon runners, where 10 weeks of intermittent or continuous aerobic training (40 km per week) increased gene expression of TLR-4 and 7 in PBMCs, regardless of systemic benefits (reduction of ox-LDL) and body weight [34]. However, a recent study showed that vigorous HIIT downregulated TLR-4/MyD88/NF-κB axis and reduced TNF-α production by peripheral monocytes of obese men [75]. Exercise training also modulates the functional activities of immune cells of obese individuals. In this sense, Baturcam and coworkers [76] described lower expression of CCR5 and RANTES in subcutaneous adipose tissue, despite no changes in the phenotype of circulating monocytes and lymphocytes in obese individuals after exercise training, suggesting the impact of chronic exercise on leukocyte chemotaxis. Recent data shed light on physical activity effects on monocyte tethering and migration in obesity. A higher physical activity pattern in obese individuals was associated with reduced migration and tethering of CD16+inflammatory monocytes, despite little effect on chemokine receptor expression [77].

Other intensities of continuous aerobic training have also been demonstrated as possible strategy for immunological modulation. For example, no change in total monocyte and lymphocyte count and percentage of TCD4⁺and TCD8⁺cells was found after 6 months of light to moderate intensity aerobic training (40 minutes of treadmill at 50 to 60–65% $\dot{V}O_{2peak}$) in sedentary subjects [78]. On the other hand, 12 weeks of moderate-intensity deep water running training increased the peripheral frequency of CD4 + and CD8 + T-cells in association with higher adiponectin and lower cortisol levels in overweight-obese women, suggesting changes in neuroendocrine axis by exercise training may impact the proportions of peripheral lymphocytes [79]. Similarly, 12 weeks of combined endurance plus strength training increased the frequencies of CD4 + and CD8 + T cells through changes in body fat composition [71]. The enhancement in T cells frequencies after exercise training may be linked with the modulatory effects of exercise training on BDCA-1 + dendritic cells phenotype of obese individuals, which prime the cellular adaptive immunity response [80]. Interestingly,

▶ **Table 2** Effects of chronic exercise on the phenotype and function of systemic monocytes and lymphocytes in obese, overweight, and sedentary humans.

Design	Exercise protocol	Results	Other information
Barry et al. (2018) [69] 2 groups (30 to 65 y) • Sedentary and obese (n = 16, 2 M + 14 F, 50.4 y), HIIT group. • Sedentary and obese (n = 17, 3 M + 14 F, 43.8 y), MICT group.	• 2 weeks of HIIT or MICT, 5 days/week. • HIIT protocol: 4 × 1 min to 10 × 1 min intervals (90 % HRmax) interspersed with 1 min recovery periods at low intensity. • MICT: ~65 % HRmax progressing from 20 min to 50 min.	• After training (basal): There were no differences in the IL10R1 or IL6Rα expression or CD14 + monocyte and T cell count.	• After training (basal): There were no changes in % body fat. • There were no changes in IL-6, IL-10, and TNF-α plasma levels. • In a whole blood culture model, HIIT and MICT reduced the ability of IL-10 to decrease TNF-α levels after LPS stimulation, however, HIIT was more potent.
Barry et al. (2017) [68] 2 groups (30 to 65 y) • Sedentary and obese (n = 19, 2 M + 17 F, 48.6 y), HIIT group. • Sedentary and obese (n = 18, 3 M + 15 F, 44.7 y), MICT group.	• 2 weeks of HIIT or MICT, 5 days/week. • HIIT protocol: 4 × 1 min to 10 × 1 min intervals (90 % HRmax) interspersed with 1 min recovery periods at a low intensity. • MICT: ~65 % HRmax progressing from 20 min to 50 min.	• After training (basal): There were no differences in monocyte and lymphocyte count. • HIIT: increase in CD14 + CD16- and CD14 + CD16 + monocytes and T cells expressing CCR5. • MICT: decrease in CD14 + CD16 + monocytes expressing CCR2 or CXCR2. • Both: decrease in CD14 + CD16- monocytes expressing CXCR2.	• There were no changes in % body fat, leptin, and chemokine plasma levels between groups and after HIIT and MICT.
Soltani et al. (2020) [90] 2 groups (F, 18 to 25 y) • Young sedentary overweight/obese (n = 15, 21.3 y), exercise group (EG). • Young sedentary overweight/obese (n = 15, 20,7 y), control group.	• 2 weeks (10 sessions) of combined training. • EG: 2 strength exercise sessions at 40–50 % progressing to 50–60 % 1RM, and 2 aerobic training sessions at 60–70 % progressing to 80–90 % HRmax. • Control group: no intervention	• After training (basal), PBMCs: There were no significant changes in TLR-4, NF-κB, and IRF3 expression.	• After training (basal): There were no changes in % body fat, and TC, TG, HDL-c, and LDL-c plasma levels. • Decrease in insulin plasma levels and HOMA2-IR and increase in VO_{2peak} in the EG.
Habermann et al. (2015) [82] 4 groups (F, 50 to 75 y) • Overweight/obese, sedentary and postmenopausal (n = 439). • Exercise group (EG) (n = 117, 59.1 y). • Diet group (DG) (n = 118, 57.9 y). • Exercise + diet group (EDG) (n = 117, 58.4 y). • Control group (n = 87, 57.1 y).	• 12 weeks of continuous aerobic training • EG: 45 min of moderate (60 to 70 % of HRmax) to high (70 to 85 % HRmax) intensity, 5 days/week • DG: reduced calorie weight loss diet • EDG: exercise plus diet. • Control group: no intervention	• After intervention (basal), PBMCs: There were no changes in the DNA repair capacity, however, when stratified by weight loss, women with highest gain in VO_{2max} in the EDG showed greater DNA repair capacity.	• After intervention (basal): There was a reduction in % body fat in all groups, except the control group. Increase in VO_{2peak} in the EG and EDG.
Campbell et al. (2008) [91] 2 groups (M, 50 to 75 y) • Postmenopausal, overweight or obese, sedentary (n = 53, 60.5 y), exercise group (EG). • Postmenopausal, overweight or obese, sedentary (n = 62, 60.9 y), stretching control group (CG).	• 12 months of combined training or stretching. • EG: Progressed to at least 60–75 % of HRmax for 45 min of treadmill walking and stationary bicycling + two sets of 10 repetitions of five exercises (upper and lower limb), 5 days/week. Fatigue was recommended, but not required. • CG: 60 min of stretching and relaxation sessions, 1 day/week.	• After intervention (basal): There were no differences between groups in T-lymphocyte proliferation, counts, and % of T cells (CD3 +, CD4 +, CD8 +) after 3 and 12 months.	• After intervention (basal): Increase in VO_{2max} and reduction in % body fat in EG after 12 months.

Design	Exercise protocol	Results	Other information
Markofski et al. (2014) [13] 3 groups • Overweight or obese, sedentary (n = 14, 59.9 y), exercise group (EG). • Overweight or obese, sedentary (n = 12, 56.7 y), exercise + energy-restricted diet group (R-EG). • Physically active, lean-to-overweight (n = 9, 6 M + 3 F, 60.1 y), control group (CG).	• 12 weeks of diet and/or strength training. • EG and R-EG: 3 sets of 8 (first set) and 12 repetitions (second and third sets) at 70 to 80 % of 1RM in eight exercises (upper and lower limb), 3 times/week. • R-EG: energy-restricted diet, 750 kcal days below their energy need • CG: no intervention	• Baseline (basal): Higher CD14 + CD16 + monocyte % in sedentary (EG and R-EG) than CG and obese than overweight (sedentary stratified by BMI). • After-intervention: decrease in CD14 + CD16 + % in EG (only overweight, not the obese subgroup) but not R-EG (neither overweight nor obese subgroup). • There were no differences in the % of CD14 + CD16 + or CD14 + CD16 − positive for TLR-4.	• Baseline (basal): Higher VO$_{2peak}$ in CG than sedentary individuals (EG and R-EG). Lower cholesterol in CG than sedentary individuals. • After intervention: decrease in % body fat in R-EG, but not in EG. Increase in VO$_{2peak}$ in sedentary. • EG but not R-EG had higher cholesterol than CG. There were no differences in the adiponectin.
Da Silva et al. (2019) [86] 2 groups (M) • Sedentary overweight (n = 15, 24.5 y), traditional high-intensity strength training group (ST). • Sedentary overweight (n = 15, 25.5 y), low-load strength training with blood flow restriction group (ST-BFR).	• 8 weeks of strength training, 3 times/week. • ST: 4 sets of 8 repetitions at 80 % 1-RM (elbow flexion and knee extension). • ST-BFR: 4 sets of 23 repetitions at 30 % of 1-RM (elbow flexion and knee extension).	• After training (basal), monocytes: increase in CD14 + CD16- % and decrease in CD14-CD16 + % in ST. • Decrease in CD16 expression on CD14 + in ST. Additionally, CD16 expression on CD14 + was lower in ST than ST-BFR. • There were no differences in the variables in ST-BFR.	• After training: There were no changes in % body fat and glucose, TG, cholesterol, HDL-c, and LDL-c plasma levels. • In whole blood culture, after stimulation with LPS or unstimulated blood, TNFα production was reduced in ST, but not in ST-BFR.
Quiroga et al. (2020) [89] 2 groups (7 to 12 y) • Obese pediatric (n = 25), exercise group (EG, 13 M + 12 F, 11 y). • Obese pediatric (n = 14), control obese group (CO, 7 M + 7 F, 10.5 y). • Healthy control (n = 14, 7 M + 7 F, 9.5 y), healthy control group (HC).	• 12 weeks of combined training, 2 times/week. • EG: Sprint of 30 s on a cycle ergometer + 5 exercises (upper and lower limb), 3 sets of 12 to 8 repetitions with a load of 30 to 70 % 1RM + elliptical cardiovascular exercise for 7 min at 50 rpm (4 min of low-medium and 3 min of high-medium load). CO and HG: no intervention.	• After training (basal), PBMCs: reduction in NLRP3, caspase-1, and osteopontin protein expression in EG. • There was no difference in the TLR-4 protein expression in EG, however, it increased in CO.	• Before training (basal): higher *Proteobacteria* and *lower Actinobacteria phyla* number in obese children (EG and CO) than HC. • After training (basal): reduction in *Proteobacteria* and *Gammaproteobacteria phyla* number, glucose plasma levels and glutamate-oxaloacetate transaminase and lactate dehydrogenase activities in EG. • There were no differences in anthropometric data throughout the study (data not shown).
• Farinha et al. (2015) [83] • 1 group (F, 40 to 64 y) • Sedentary middle-aged (n = 23, 51.7 y)	• 12 weeks of running/walking on the treadmill with progression of volume and intensity (30 to 60 minutes at 50 to 70 % of HRreserve).	• After training (basal), PBMCs: There were no differences in the IL-1β, TNF-α, IFN-γ, IL-10, IRS-2, and MMP-9 mRNA expression.	• After training (basal): increase in VO$_{2peak}$ and decrease in body fat mass and creatinine plasma levels. • There were no changes for glucose, TC, TG, and HDL-c plasma levels. • Increase in IL-10, TBARS, and AOPP plasma levels and reduction in IL-1β, IL-6, INF-γ, TNFα, and T-SH plasma levels.
Streese et al. (2020) [72] 2 groups (50 to 80 y) • Sedentary with cardiovascular risk factors (n = 40, 22 M + 18 F, 59 y), exercise group (EG). • Sedentary with cardiovascular risk factors (n = 34, 14 M + 20 F, 58 y), control group (CG).	• 12 weeks of HIIT, 3 times/week. • EG: HIIT consisting of 4 × 4 minutes at 80–90 % HRmax with 3 min of active recovery at 60–70 % HRmax. • CG: Received physical activity recommendations.	• After training (basal), PBMCs: decrease in mitochondrial adaptor p66^{Shc} gene expression and increase in p66Shc gene promoter methylation in EG than CG.	• After training: decrease in body fat and LDL-c plasma levels, and increase in VO$_{2max}$ in EG. • There were no changes for HDL-c and glucose plasma levels.

▶ **Table 2** Continued.

Design	Exercise protocol	Results	Other information
Ibrahim et al. (2018) [92] 4 groups (M, 19 to 26 y) ■ Healthy sedentary (n = 12, 21 y), circuit training + placebo group (EG). ■ Healthy sedentary (n = 9, 22 y), circuit training + probiotics group (P-EG). ■ Healthy sedentary (n = 10, 22 y), placebo control group (CG). ■ Healthy sedentary (n = 10, 23 y), probiotics control group (P-CG).	■ 12 weeks of circuit training, 3 times/week ■ EG and P-EG: 2 circuits (weeks 1–8) followed by 3 circuits (weeks 9–12) with each circuit comprising 10 stations in 11 exercises (upper and lower limb), with 30 seconds and rested for 1 min. The intensity of circuit training was estimated by referring to the post-exercise HR. ■ CG and P-CG: no intervention.	■ After training (basal): There were no differences in total lymphocytes, T lymphocytes, and TCD4 + and TCD8 + cell count between groups. ■ Increase in total lymphocytes, T lymphocytes, and TCD4 + count in EG. ■ Increase in TCD8 + cell count in EG, P-EG, and P-CG.	After training (basal): There were no differences in % body fat and salivary antimicrobial proteins
Bartlett et al. (2017) [70] 2 groups (18 to 60 y) ■ Healthy sedentary (n = 14, 4 M + 10 F, 42 y), high-intensity interval training group (HIIT). ■ Healthy sedentary (n = 13, 5 M + 8 M), moderate-intensity continuous training group (MICT).	■ 10 weeks of HIIT or MICT, 3 times/week. ■ HIIT: 15 to 60 seconds of repeated sprints on the bike at > 90 % HRmax, interspersed with periods of active rest (45–120 seconds). ■ MICT: 30 to 45 minutes of cycling at ~70 % HRmax	■ After training (basal), monocytes: increase in CD14 + CD16 −, phagocytosis, and percentage of monocytes producing an oxidative burst in both protocols. ■ Decrease in CD14 + CD16 + % in both groups. Decrease in CD14 + CD16 + + % in HIIT but not in MICT. ■ Decrease in TLR-4 expression in CD14 + CD16 + + and TLR-2 expression in CD14 + CD16 + in both groups. ■ There were changes in monocyte and lymphocyte count.	■ After training (basal): increase of VO$_{2peak}$ in both groups. Decrease of body fat % in MICT. ■ Increase of phagocytosis and ROS synthesis in both groups. ■ There were no changes for IL-1β, IL-6, IL-8, IL-17, TNFα, CRP, GM-CSF, IL-4, IL-10, IL-13, adiponectin, and cortisol plasma levels. ■ Decrease in leptin plasma levels in MICT, but not in HIIT.
Colato et al. (2014) [71] 1 group (M and F above 18 y) ■ Sedentary obese (n = 14)	■ Concurrent training is described as the execution, in the same training session, of both aerobic and strength exercises ■ The training sessions were divided into three parts: (1) warm-up exercises; ■ (2) concurrent training; ■ (3) stretching. The duration of each training session was 60 minutes. Strength training was based on the method of alternating segments with the following exercises: bench press with dumbbells plan; squats; shoulder abduction; plantar flexion; horizontal pulley; and abdominal crunch. During training, a progression of intensity was applied (50–75 % 1-RM) as well as a decrease in the number of repetitions in all exercises, except for abdominal and plantar flexion.	■ The participants had increased frequencies of CD3 + CD4 + and CD3 + CD8 + T lymphocytes and a reduction in the frequencies of HLA-DR + monocytes.	■ After 12 weeks of training reductions in body weight, body mass index, waist, abdomen, and hip circumferences and percentage mass of fat were observed. ■ Increase in the time taken to reach exhaustion.

Design	Exercise protocol	Results	Other information
Colato et al. (2017) [79] 2 groups (F) ▪ Sedentary overweight-obese exercise (n = 11, 48,77 y ± 12.87 y) ▪ Sedentary overweight-obese control (matched-age, n = 9)	▪ Individuals completed three sessions of deep-water running per week for 12 weeks, with 1–2 days of rest between each session. ▪ Each session had the duration of 70 minutes, including initial warm up, training (60 minutes), and final stretching. The perceived exertion was used as an intensity indicator of aerobic exercise.	▪ Peripheral frequency of T Lymphocytes before and after 12 weeks of deep-water running training, a significant increase in CD3 + CD8 + T cells was observed, with no differences in CD3 + CD4 + T cells. ▪ CD8 + and CD4 + T cells were higher after deep-water running training compared to control group.	▪ After training, serum adiponectin, IL-10, and TNF-α significantly increased by approximately 4.95 %, 17.6 %, and 47 % respectively, with higher TNF-α levels after training compared to control group. ▪ Salivary cortisol levels reduced after 12 weeks of deep-water running training. ▪ Although there were no significant changes in IL-6, lA, INF- γ, or ghrelin.
Woods et al. (1999) [78] 2 groups (no gender distribution reported) ▪ Sedentary older adults (n = 14, 64.4 y), aerobic exercise group (EG) ▪ Sedentary older adults (n = 15, 65.5 y), control group (CG).	▪ 6 months of light to moderate aerobic training, 3 times/week. ▪ EG: 10–15 to 40 minutes of treadmill at 50 % to 60–65 % VO_{2peak}. ▪ CG: Wide array of large muscle group stretching and light resistance exercises against rubber tubing, 40 min per session. ▪ Blood collection was performed before and after intervention, at rest and after an acute test session on a treadmill until voluntary fatigue.	▪ After-training (basal): There were no differences in total lymphocytes and monocytes total counts, and % and number of CD3 +, CD4 +, and CD8 + T cell. ▪ Before and after-training (acute response): increase in monocyte and lymphocyte count in both groups. Increase in CD3 +, CD4 +, and CD8 + T cell count. Decrease in %CD4 + and increase in %CD8 + (decrease in CD4/CD8 ratio) in both groups. ▪ Increase in T-cell proliferative response to mitogenic stimulation in both groups post-intervention, however, EG was greater than CG.	▪ After training (basal): Decrease in body weight, but not in % body fat in EG. Increase in VO_{2peak} in both groups, however, EG was greater than CG.
Schaun et al. (2011) [88] 2 groups (M, 54 ± 4 y)Sedentary middle-aged (n = 10), concurrent training group (CT). Sedentary middle-aged (n = 10), continuous training of moderate intensity group (MICT).	12 weeks of combined training or MICT, 3 times/week. CT: 20 min of cycling at 65 % to 80 % HRreserve + ~15 min of 8 strength exercises (upper and lower limb) equivalent to 15RM to 8RM. MICT: 30 min of cycling at 65 % HRreserve.	After training (basal): There were no differences in the monocyte phagocytic index.	After training (basal): increase in VO_{2peak} and decrease in % body fat in CT, but not in MICT. Increase in HDL and decrease in glycaemia, LDL plasma levels, and CT/HDL ratio in CT. Decrease in glycemia and CT/HDL ratio in MICT. Increase in % vascular dilation in MICT, but not in CT.
LaPerriere et al. (1994) [73] 2 groups (M, 18 to 40 y) ▪ Sedentary (n = 7, 30 y), continuous training of moderate intensity group (MICT). ▪ Sedentary (n = 7, 31.1 y), control group (CG).	▪ 10 weeks of MICT, 3 times/week. ▪ MICT: 45 min of cycling at 70 to 80 % HRmax. ▪ CG: no intervention.	▪ After training (basal): There were no changes in the monocytes and lymphocytes %. ▪ Increase in ↑ CD2 +, CD2 + TAI +, CD4 +, CD45RA + CD4 + and CD8 + lymphocyte phenotype counts in MICT than in CG.	▪ After training (basal): Increase in VO_{2peak} in MICT. There was no change in the body composition.
Timmerman et al. (2008) [93] 2 groups (65 to 80 y) ▪ Sedentary (n = 15, 4 M + 8 F, 71 y), training group (TG). ▪ Physically active (n = 15, 8 M + 7 F, 70.9 y), control group (CG).	▪ 12 weeks of combined training, 3 times/week. ▪ TG: 20 minutes of treadmill walking at 60 % to 70 % of HRreserve + 2 sets of 8 (first set) and until 15 repetitions (second set) at 70 to 80 % 1RM in 8 resistance exercises (upper-body and lower-body). ▪ CG: no intervention.	▪ Before training (basal), mono-cytes: Higher CD14 + + CD16 + % in the TG than the CG. Higher unstimulated TNF-α production per CD14 + monocyte in the TG than the CG. ▪ After training: Decrease in CD14 + CD16 + monocyte % in the TG (tendency). ▪ Decrease in unstimulated and stimulated TNF-α production per CD14 + monocyte in the TG. ▪ There were no differences in TLR-4 expression in CD14 + (classical monocytes).	▪ Before training (basal): Lower CRP plasma levels and % body fat and higher VO_{2peak} in CG than TG. ▪ After training (basal): There were no changes in the % body fat and CRP plasma levels. Increase in VO_{2peak} in the TG, equaling with CG. ▪ Correlations between pre-post change in CD14 + CD16 + % and pre-post change in LPS-stimulated TNF-α production (when TG and CG were combined).

▶ **Table 2** Continued.

Design	Exercise protocol	Results	Other information
Bartholomeu-Neto et al. (2015) [87] 2 groups (F) • Sedentary older adults (n = 28, 70.6 y), exercise group (EG). • Sedentary older adults (n = 26, 72 y), control group (CG).	• ~8.6 months of strength training, 3 times/week. • EG: 3 sets of 12 repetitions at 70 % 1RM in 9 resistance exercises (upper-body and lower-body). • CG: They remained sedentary and performed occupational activities unrelated to physical activity offered by the health education program.	• After training (basal): There were no differences in monocytes phagocytic index and reactive oxygen species production in the monocytes.	• After training (basal): Decrease in TNF-α and IL-6 plasma levels in the EG. • Increase in phagocytic index in neutrophils in the EG than the CG. There was no change in reactive oxygen species production in the neutrophils.
Coen et al. (2010) [94] 3 groups (40 to 65 y) • Hypercholesterolemic and sedentary (overweight or obese): 20 weeks of rosuvastatin • Calcium group (R) (10 mg/d) treatment (n = 17, 9 M + 8 F, 52.1 y). • Hypercholesterolemic and sedentary (overweight or obese): same rosuvastatin treatment with the last 10 weeks including exercise training group (RE) (n = 16, 7 M + 9 F, 52.2 y). • Hypercholesterolemic physically active subjects (control): No intervention (n = 16, 7 M + 9 F, 51.6 y)	• Combined training, 3 d/wk. • Endurance protocol: 20 minutes of treadmill walking at 60 % to 70 % of HRreserve. • Strength protocol: 2 sets of up to 12 repetitions at 70 % to 80 % 1RM in 8 exercises (upper-body and lower-body).	• Percentage of CD14 + monocytes expressing TLR-4 was not different between and within R, RE, and control throughout the study • More TLR-4 expressed in CD14 + CD16 + than CD14 + CD16- monocytes in both groups • After intervention (basal): Higher TLR-4 expression in CD14 + monocytes after treatment in R • Lower % of CD14 + CD16 + monocytes in RE group.	• Before training (basal): There were no significant differences in % body fat between the R and RE groups. Lower % body fat and higher VO$_{2peak}$ in the control group than the R and RE. • After training (basal): Increase in VO$_{2peak}$ in the RE. There were no significant changes in % body fat over time • Lower CRP in the RE compared to the R group after intervention.
Nickel et al. (2011) [34] 3 groups (M, 30 to 60 y) • Obese amateur marathon runners (ONE) (n = 15, 40 y) • Lean non-elite (LNE) (n = 16, 40 y) • Lean elite (LE) (n = 16, 40 y)	• Chronic endurance training. • 10 weeks, 4d/wk of continuous endurance and interval training. • Intensity given by individual target HR. • ONE and LNE: 40 km/wk; LE: 55 km/wk.	• Before training (basal), PBMCs: There were no differences in the TLR-2, 4, and 7 mRNA expression. • After training (basal): higher TLR-2 mRNA in LNE, upregulation of TLR-4 and 7 mRNA in PBMCs of all groups. • No exercise-induced changes in MyD88 mRNA gene-expression in PBMCs between the groups. • In LNE, increase in TLR-4 and 7 protein expression in PBMCs after training, no change in TLR-2 and MyD88. No protein analysis in ONE and LE.	• Although both groups reduced body weight after training, only LNE and LE reduced the % body fat. The ONE had a downward trend. The obese group achieved a tendency to reduce fat (p = 0.058). • Before training (basal): higher oxLDL plasma levels in ONE compared to LE. Higher adiponectin plasma levels in LE compared to ONE. Higher IL-6 and TNF-α plasma levels in LNE and ONE compared to LE. • After training (basal): oxLDL plasma levels reduced in ONE. oxLDL plasma levels increased in LE. Adiponectin plasma levels increased in LNE.

Design	Exercise protocol	Results	Other information
Soltani et al. (2020) [75] 2 groups (F, 10 to 25 y) ▪ Combined HIIT (n = 13) ▪ Control (n = 13)	▪ The training protocol consisted of a progressive all-extremity cHIIT. ▪ Including 4 sets of 4-min intervals separated by 3 periods of 3-min intervals of active rest (leg cycling) (▶ **Fig. 2**). Each interval involved 4 exercises, i. e., 2 aerobic exercises (arm and leg simultaneous cycling. ▪ 2 resistance exercises (1 upper body and 1 lower body exercise; according to a circuit training program where an RT followed all-extremity cycling training.	▪ CHIIT intervention induced lower expression of TLR-4 in the cHIIT compared to both pre-intervention ▪ Statistical decrease observed at the MyD88 level in the cHIIT compared to the control ▪ NF-κB and IRF3 gene expression significantly decreased after cHIIT intervention compared to pre-intervention.	▪ Decrease in body fat, waist circumference, and BMI ▪ Statistically significant increase of 24.48 % in cardiorespiratory fitness ▪ TNFα levels decreased significantly in cHIIT from pre-intervention to post testing and compared to the control group.
Baturcam et al. (2014) [76] 2 groups (M and F, 35 to 45 y) ▪ Lean (6 M + 11 F) ▪ Obese (22 M + 18 F)	▪ Each exercise session included 10 minutes of warming-up and cooling down steps at 50–60 % of max HR, along with 40 minutes of the prescribed exercise program at 65–80 % of max HR. ▪ For the duration of the 3-month period, participants exercised 3 to 5 times per week and they were instructed to reach and maintain the recommended heart rate range. This was achieved by regular monitoring of the heart rate during the aerobic training. Strength training was performed 2 to 3 times a week according to the program plan.	▪ Significant increase in RANTES and CCR5 expression in the subcutaneous adipose tissue of obese compared to lean. ▪ In PBMCs, however, while the levels of RANTES mRNA and protein were comparable between groups, CCR5 mRNA was downregulated in obese subjects.	▪ Physical exercise significantly reduced the expression of both RANTES and CCR5 in the adipose tissue of obese individuals with a concomitant decrease in the levels of the inflammatory marker's TNF- α, IL-6, and p-JNK. ▪ Circulating RANTES correlated negatively with anti-inflammatory IL-1ra and positively with proinflammatory IP-10 and TBARS levels.
Wadley et al. (2021) [77] 2 groups (M, 30 to 46 y) ▪ Lean (n = 12) ▪ Obese (n = 12)	▪ 60-minute session of walking exercise at 60–65 % of their $\dot{V}O_{2peak}$. Walking intensity was confirmed using a portable metabolic cart which analyzed breath-by-breath gases and subjective measures of perceived exertion were obtained using the Borg Scale (6–20).	▪ Monocyte subsets (total, classical, intermediate, and CCR2 + monocytes) were greater in obese vs. lean. ▪ Adjustments for physical activity mitigated group differences for glucose, lipids, and monocyte subsets. ▪ Ex vivo tethering and migration (absolute and relative) of most monocyte subsets was greater in obese vs lean. ▪ Relative monocyte tethering and migration were largely not influenced by physical activity.	▪ Metabolic (glucose and lipids) and inflammatory (C-reactive protein) markers were greater in obese vs. lean (lower high-density lipoprotein).

▶ **Table 2** Continued.

Design	Exercise protocol	Results	Other information
van der Zalm et al. (2020) [81] 2 groups (M and F, 30 to 53 y) ▪ Obese (n = 27) ▪ Control (n = 17)	▪ The physical exercise contained a combination of aerobic endurance training and anaerobic resistance training, with the aim of stimulating exercise in the home-setting and improving both cardiorespiratory and muscular fitness. ▪ Between sessions patients were offered homework to promote their active participation in the program, as well as to explore how they can organize their lifestyle in a healthier and more personalized way. ▪ Data of the participants were collected before the intervention as well as 10 weeks and 75 weeks after the start of the intervention.	▪ sIL-2R and sCD163 levels were higher in obese than controls ▪ After intervention, sIL-2R decreased while peripheral Treg frequencies increased within the reference range.	▪ sCD163 did not change significantly upon intervention, nor did the cytokines, chemokines, and growth factors (except IP-10/ CXCL10).

Note: MICT: moderate-intensity continuous training, HIIT: high-intensity intermittent training, HRmax: heart rate maximum, VO_{2peak}: peak oxygen consumption, RM: maximum repetition, CCR5: C-C chemokine receptor type 5, CCR2: C-C chemokine receptor type 2, CXCR2: C-X-C motif chemokine receptor 2, CXCL10: C-X-C motif chemokine ligand 10, HOMA2-IR: Homeostasis Model Assessment 2 for insulin resistance, IRF3: interferon regulatory factor 3, TG: triacylglycerol, TC: total cholesterol, HDL: high-density lipoprotein, LDL: low-density lipoprotein, NLRP3: NLR family pyrin domain containing 3, IRS-2: insulin receptor substrate 2, MMP-9: matrix metalloproteinase-9, TBARS: thiobarbituric acid reactive substance, AOPP: advanced oxidation protein products, T-SH: total thiol, MyD88: myeloid differentiation factor 88, CRP: C-reactive protein, JNK: c-Jun N-terminal kinase, sCD163: soluble cluster differentiation 163, IP-10: Interferon-inducible protein 10, GM-CSF: granulocyte-macrophage colony-stimulating factor, IL-: interleukin, TNF-α: tumor necrosis factor-alpha.

HIIT is linked to strong immunoregulatory actions and one-week of HIIT increased CD39 + Treg phenotype in sedentary obese men [21]. Furthermore, increases in structured physical activity program increased Treg frequency without changes in body composition of obese individuals who engaged in lifestyle change program [81].

After 12 weeks of aerobic training (45 min at 60–70 to 70–85 % HRmax), the DNA repair ability in PBMCs was not altered in overweight/obese sedentary individuals [82]. Similarly, 12 weeks of walking/running (30 to 60 minutes at 50 to 70 % of HRreserve) did not promote changes on gene expression of IL-1β, TNF-α, IFN-γ, IL-10, insulin receptor substrate 2 (IRS-2) and matrix metalloproteinase-9 (MMP-9) in PBMCs of sedentary individuals. However, there was an increase in the systemic anti-inflammatory profile and a reduction in body fat after training [83]. Therefore, these findings suggest the need to use methods more accurately to assess the functionality of cells, for example secretion of cytokines associated with protein expression, in which could detect possible changes after the training period.

Resistance training is practiced worldwide and used as a strategy not only to induce skeletal muscle adaptations (hypertrophy and strength), but also is an important protective factor against chronic diseases [84, 85]. Markofski et al. [13] applied 12 weeks of strength training in overweight or obese sedentary individuals. The authors showed an increase in the population of intermediate monocytes only in overweight but not in obese individuals, with no changes in the percentage of monocytes expressing TLR-4. Additionally, after traditional strength training or with flow restriction (4 sets of 23 repetitions at 30 % of 1-RM), sedentary overweight in-

dividuals showed beneficial effects on monocyte subtypes [86]. In this study, there was a reduction in the percentage of non-classical monocytes and expression of CD16 in CD14⁺ monocytes, as well as an increase in the percentage of classical monocytes only in the group that performed the traditional training. The benefits of these changes were confirmed by reduction in the production of TNF-α with or without LPS stimulation [86]. On the other hand, the phagocytosis index and production of reactive oxygen species were not altered in PBMCs of sedentary individuals after traditional strength training [87]. Therefore, traditional strength training may be a good strategy for immunological modulation. However, some studies present limitations regarding different T lymphocyte subpopulations.

The combined exercise training (aerobic and strength) program also has been demonstrated be an alternative strategy to optimize the adaptations of both modalities. After 12 weeks of combined training, no differences were found on monocyte phagocytosis capacity [87, 88], expression of TLR-4, NF-kB and interferon regulatory factor 3 (IRF3) in PBMCs [89, 90] and no difference on T lymphocyte proliferation and CD3⁺, CD4⁺and CD8⁺number [91, 92]. On the other hand, a reduction in the expression of NLRP-3, caspase 1 and osteopontin was found in PBMCs of obese individuals after 12 weeks of combined training, 2 times/week [89]. Additionally, sedentary individuals after 12 weeks of combined training (3 times/week) demonstrated lower production of LPS-stimulated TNF-α in whole blood culture [93]. Interestingly, the same study showed that the overall reduction in the percentage of intermediate monocytes was positively correlated with the overall reduction in LPS-stimulated TNF-α in whole blood culture. Corroborating

▶ **Table 3** Effects of chronic training on the number and function of systemic monocytes and lymphocytes in humans with T2DM, insulin resistant, and metabolic syndrome.

Design	Exercise protocol	Results	Other information
T2DM or insulin resistant			
Reyna et al. (2013) [97] ▪ 3 groups (no gender distribution reported) ▪ Sedentary and lean (LE) (n = 17, 39 y) ▪ Obese (OB) (n = 8, 40 y) ▪ T2DM (n = 11, 50 y)	▪ 15 consecutive days of chronic aerobic training (cycle ergometer) ▪ Each session consisted of 4 x 8 min at 70 % VO_{2peak} followed by 2 min of rest, (40 min/d.).	▪ Before intervention (basal, PBMCs): higher TLR-4 protein content in T2DM and a tendency to OB compared to the LE. Higher ERK2 phosphorylation in T2DM compared to the LE. ▪ There was no difference for TLR-2, JNK phosphorylation, and NF-κBp65 protein content between groups. ▪ After training (basal, PBMCs): There was no change in TLR-2, TLR-4, ERK, and JNK phosphorylation, and NF-κBp65 protein content in any group.	▪ Before training (basal): higher NEFA, HbA_{1c}, glucose, hs-CRP, endothelin-1, and sICAM-1 levels in T2DM compared to the LE. Higher NEFA, HbA_{1c}, and glucose in T2DM compared to the OB. Higher insulin levels in T2DM and OB compared to LE. T2DM, and OB were insulin resistant compared to the lean. ▪ After training (basal): There were no changes in weight, HbA_{1c}, NEFA, glucose, and insulin plasma levels in the OB and T2DM. ▪ Increase in VO_{2peak} and insulin sensitivity in both groups.
Liu et al. (2015) [101] 3 groups (no gender distribution reported) T2DM + conventional therapy + exercise (T2DMe) (n = 22, 52.6 y) T2DM, conventional therapy (T2DMc) (n = 20, 52.6 y) Healthy control (control) (n = 20, 51.2 y)	▪ Combined training ▪ T2DMe: aerobic exercise 12 weeks, 3d/wk, 10–30 min at 40–60 % VO_{2peak} + strength exercise 2–3d/wk, 2 sets of 8–10 repetitions at 50–60 % 1RM ▪ T2DMc: drug therapy and diet control ▪ control: No intervention	▪ Before intervention (basal, PBMCs): higher TLR-4 mRNA and protein content in T2DMe and T2DMc than in control. ▪ After exercise intervention (basal, PBMCs): TLR-4 mRNA and protein content were lower in T2DMe than in T2DMc.	▪ Before intervention (basal): There were no differences for glucose, insulin, HbA_{1c}, HOMA-IR, TG, TC, HDL, and LDL levels between the T2DMe and T2DMc groups. Higher IL-18 and lower IL-33 levels in T2DMe and T2DMc than in control. ▪ After intervention (basal): decrease in glucose, insulin, and HbA_{1c} in the T2DMc and T2DMe. Decrease in HOMA-IR in the T2DMe. ▪ Glucose, insulin, HOMA-IR, HbA_{1c}, and IL-18 were lower in T2DMe than the T2DMc.
Robinson et al. (2015) [96] 2 groups (30 to 65 y) ▪ Sedentary, overweight/obese, pre-diabetics (n = 20, 3 M + 17 F, 52 y), group HIIT. ▪ Sedentary and overweight/obese, pre-diabetics (n = 19, 4 M + 15 F, 52 y), group MICT.	▪ 2 weeks of HIIT or MICT, 5 days/week. ▪ HIIT protocol: 4 × 1 min to 10 × 1 min intervals (90 % HRmax) interspersed with 1 min recovery periods at a low intensity. ▪ MICT: ~65 % HRmax progressing from 20 min to 50 min.	▪ After training (basal): reduction in TLR-4 expression on lymphocytes and monocytes after both HIIT and MICT. ▪ Reduction in TLR-2 expression on lymphocytes after both HIIT and MICT. ▪ There were no changes in CD14 + monocyte and lymphocyte count.	▪ After training (basal): Small body fat reduction and increase in VO_{2peak} in both groups. ▪ There were no changes in HOMA-IR, HOMA-β, and insulin, NEFA, IL-6, IL-10, and TNF-α plasma levels. ▪ Decrease in fructosamine plasma levels after HIIT and MICT. ▪ Decrease in plasma glucose in the MICT but not HIIT.
Wenning et al. (2013) [98] 1 group (M, 47 to 77 y) ▪ Overweight, non-insulin dependent T2DM (n = 14, 61 y).	▪ 12 weeks of aerobic training, 2 times/week. Progression from 15 to 45 min of cycling at an HR corresponding to a 2 mmol/l lactate threshold	▪ After training (basal): There were no differences in monocytes, CD8 + and CD4 + T cells, and T cell subpopulations (Treg, memory and naïve).	▪ After training (basal): Decrease in BMI and weight. ▪ Decrease in resistin, LDL-c, and TC plasma levels. There were no changes in the HOMA-IR and insulin, glucose, HDL-c, and TG plasma levels.

▶ **Table 3** Continued.

Design	Exercise protocol	Results	Other information
Annibalini et al. (2017) [102] 2 groups (M, 50 to 70 y) ■ Overweight with T2DM (n = 8), exercise group (EG, 57 y). ■ Overweight with T2DM (n = 8), control group (CG, 60 y).	■ 16-week combined training, 3 times/week. ■ EG: Walking on a treadmill, 40 to 65 % of HRreserve, 30 to 60 minutes + 2 to 4 sets of 20 to 12 repetitions at 40 to 60 % of 1RM in 4 exercises (upper-body and lower-body). ■ CG: no intervention.	■ After training (basal), PBMCs: Decrease in IL-6 and IGFBP-3 expression in EG compared to CG. ■ Increase in IGF-1 expression in EG compared to CG. ■ There was no change for TNF-α expression.	■ After training (basal): Decrease in % body fat and increase in VO$_{2peak}$ in the EG. ■ Decrease in TC, TNF-α, IL-6, MCP-1, leptin, and RBP4 plasma levels and increase in IGF-1 plasma levels in the EG compared to CG. ■ There were no changes for adiponectin, CRP, IGFBP-3, HDL-c, LDL-c glucose plasma levels and % HbA1c.
De Matos et al. (2019) [22] 3 groups (18 to 55 y) ■ Lean insulin sensitive (n = 9, 3 M + 6 F, 29 y), control group (CG). ■ obese insulin sensitive (n = 9, 2 M + 6 F, 35 y), (OB-E). ■ obese insulin resistant (n = 9, 3 M + 5 F, 30 y), (OBR-E).	■ 8 weeks of HIIT, 3 times/week. ■ OB-E and OBR-E: 8–12 cycling exercise bouts of 60 s, at 80 to 110 % of the peak power, followed by active recovery of 60 s at 30 W. ■ CG: no intervention.	■ Before training (basal): higher % of CD14 + CD16 + in obese individuals (OB-E and OBR-E) compared to CG. There were no differences for classical and intermediate monocytes. ■ Higher HLA-DR expression in intermediate monocytes of OBR-E compared to CG. ■ After-training (basal): decrease in % CD14 + + CD16 + monocytes in OB-E and OBR-E. Increase in % intermediate monocytes in OBR-E. ■ Decrease in HLA-DR expression in intermediate monocytes from OBR-E.	■ Before intervention (basal): Higher insulin blood levels, HOMA-IR, and HOMA-β in OBR-E compared to OB-E and CG. Higher TG and VLDL-C in OBR-E compared to CG.
MetS			
Steckling et al. (2019) [106] 1 group (F, 53.87 y) ■ Postmenopausal, sedentary with MetS and obesity (n = 15).	■ 12 weeks of HIIT 3 times/week. ■ HIIT: 4 × 4-min at 90 % HRmax with 3 min active recovery at 70 % HRmax between intervals.	■ After training (basal): There were no differences in the PBMC mRNA expressions of TNF-α, NF-κBp65, IL-6, and IL-10.	■ After training (basal): increase in VO$_{2peak}$ and decrease in body weight, but not body fat mass. ■ Decrease in glucose, leptin, resistin, ghrelin, TNF-α, IL-6, IL-18, and INF-γ plasma levels and increase in adiponectin and IL-10 plasma levels.
Martins et al. (2016) [103] 2 groups (55 to 65 y) ■ MetS patients (n = 20), (5 M + 15 F, 57.9 y), exercise group (EG). ■ healthy (n = 20, 6 M + 14 F, 59.4 y), control group (CG).	■ 30 weeks of combined training 3 times/week. ■ EG: 30 to 45 min of moderate to relatively fast speed walking (measured by rating of perceived exertion) + 3 sets of 10 repetitions at 70 % of 1RM in 4 to 11 types of exercises (upper-body and lower-body). ■ CG: no intervention.	■ Before training (basal), lymphocytes: higher ATP and ADP hydrolysis (higher E-NTPDase activities) and lower ADA activities in the EG compared to CG. ■ After 15 weeks of training (basal): decrease in ATP and ADP hydrolysis and increased ADA activities in the EG. ■ After 30 weeks of training (basal): similar ATP and ADP hydrolysis and E-NTPDase and ADA activity between groups. ■ Positive correlation between E-NTPDase activities and negative correlation between ADA activities for ALT/AST ratio, CRP, and waist circumference in the EG.	■ Before training (basal): Higher BMI, CRP, glucose, TG, and LDL-c plasma levels, and lower HDL-c in the EG compared to CG. ■ After 15 and 30 weeks of training (basal): progressive decrease in BMI, CRP, glucose, TG, and LDL-c plasma levels, and increase in HDL-c in the EG. ■ After 30 weeks there were no differences in HDL-c and LDL-c blood concentrations between groups.

Note: MICT: moderate-intensity continuous training, HIIT: high-intensity intermittent training, HRmax: heart rate maximum, VO$_{2peak}$: peak oxygen consumption, RM: maximum repetition, TLR: toll-like receptor, JNK: c-Jun N-terminal kinase, NF-κB: nuclear factor kappa B, NEFA: non-esterified fatty acids, HbA1c: glycated hemoglobina, hs-CRP: high-sensitivity C-reactive protein, sICAM-1: soluble intercellular adhesion molecule-1, TG: triacylglycerol, TC: total cholesterol, HDL: high-density lipoprotein, LDL: low-density lipoprotein, IGFBP-3: soluble insulin-like growth factor binding protein-3, IGF-1: insulin-like growth factor-1, HLA-DR: human leukocyte antigen, IL-: interleukin, TNF-α: tumor necrosis factor-alpha, INF-γ: interferon-gamma.

these results, 10 weeks of combined training reduced the percentage of intermediate monocytes in sedentary individuals treated with pharmacological compound rosuvastatin, compared with individuals who only received the pharmacological compound rosuvastatin [94]. These findings demonstrate anti-inflammatory benefits by reducing the proportion of CD16 + monocytes after combined training. The differences found between the studies may be related to the characteristics of the exercise protocol performed and the high individual variability.

T2MD or insulin resistant

Some past studies hypothesized that the exercise training mode directly impact on the inflammatory milieu of T2MD and insulin resistant individuals. In this regard, Balducci and coworkers (2010)

[95] showed that high-intensity endurance training and high-intensity combined endurance plus strength training led to superior effects on the management of cytokines over 12 months in diabetic individuals. On the other hand, low-intensity endurance exercise training increased the systemic TNF-α levels concomitant to decreased IL-4 concentrations in diabetic patients. Thus, the type, intensity and mode of exercise may play a role on cell phenotype and, consequently, systemic inflammation of diabetes individuals. Robinson et al. [96] submitted pre-diabetic individuals to 2 weeks of HIIT (4 × 1 min to 10 × 1 min intervals (90 % HRmax) interspersed with 1 min active recovery) and MICT (~65 % HRmax progressing from 20 min to 50 min). After both training protocols, there was a reduction in the expression of TLR-4 over monocytes and lymphocytes and a reduction in TLR-2 over lymphocytes. Despite the reduction in circulating glucose concentrations occurring only in the MICT group, both groups showed a positive metabolic effect by reducing the systemic concentration of fructosamine [96]. Additionally, 8 weeks of HIIT (12 cycling exercise bouts of 60 s, at 80 to 110 % of the peak power) reduced the proportion of non-classical monocytes, increased the proportion of intermediate monocytes and decreased the expression of HLA-DR on intermediate monocytes of action insulin resistant individuals [22].

Nonetheless, individuals with T2DM submitted to 15 consecutive days of aerobic training (4 x 8 min at 70 % $\dot{V}O_{2peak}$ followed by 2 min of rest) showed no changes in TLR2, TLR4, ERK and JNK phosphorylation, and p65 NF-kB protein content in PBMCs [97]. In the same study, although individuals increased insulin sensitivity, there were no changes in circulating concentrations of glucose, insulin, glycated hemoglobin (HbA1c) and non-esterified fatty acids (NEFA). Similarly, after 12 weeks of continuous aerobic training (15 to 45 min of cycling at a HR corresponding to a 2 mmol/L lactate threshold), there were no changes in CD4$^+$ and CD8$^+$ T cells, subpopulations of T cells (Treg, memory and naïve), HOMA-IR and circulating concentrations of glucose, insulin, HDL-c and triacylglycerol, except for the reduction in resistin, LDL-c, and total cholesterol [98]. Of note, Reyna et al. [97] prescribed the intensity and volume of each session similar to the MICT protocol by Robinson et al. [96], however, the protocol was two-minute passive intervals during the 15 sessions, which may explain, at least in part the divergent findings between studies. Additionally, the protocol proposed by Wenning et al. [98] was performed close to 2 mmol/L lactate threshold, possibly representing a low intensity stimulus [99] and contributing to the absence of alteration of the studied T cell subpopulations. On the other hand, pre-diabetic older subjects who engaged to 3 weeks of both concentric exercise training or eccentric exercise training presented increases in the proportions CD4 + CCR7 + CD45ro + central memory cells, CD8 + CCR7 + CD45ro-naïve cells, and CD8 + CCR7 + CD45ro + central memory cells after both trainings [100]. Given the role of premature immunosenescence in the progression of T2DM, the rejuvenating effects of eccentric or concentric exercise training on peripheral T-cells may have a prominent clinical significance. Taken together, the findings suggest anti-inflammatory benefits of both HIIT and MICT on monocytes and lymphocytes.

Resistance training is an interesting strategy to assist in the prevention and control of T2MD, stimulating the reduction of the concentration of HbA1c, increasing the GLUT-4 and increasing the in-

sulin sensitivity [84]. To date, few studies have evaluated the influence of resistance training on monocytes and lymphocytes of individuals with T2DM, however, some studies have investigated the influence of combined training on PBMCs of individuals with T2DM [101, 102]. Individuals with T2DM who underwent 12 weeks of combined training (10–30 min of aerobic exercise at 40–60 % $\dot{V}O_{2peak}$ and strength exercise, 2 sets of 8–10 repetitions at 50–60 % 1RM) showed lower TLR-4 gene and protein expression compared to individuals with T2DM in pharmacological treatment (without exercise), as well as lower HOMA-IR and lower concentrations of insulin, glucose, HbA1c and IL-18 [101]. Additionally, after 16 weeks of combined training (30 to 60 minutes of walking at 40 to 65 % of HRreserve plus 2–4 sets of 20 to 12 repetitions at 40 to 60 % of 1RM), the PBMCs of individuals with T2DM and overweight individuals showed higher expression of insulin-like growth factor-1 (IGF-1) and reduced expression of IL-6 and IGF-binding protein 3 compared with the T2DM control group [102]. The same study demonstrated lower circulating concentrations of total cholesterol, TNF-α, IL-6, MCP-1, leptin and retinol binding protein 4 (RBP4) and increased IGF-1 in exercised T2DM group. Therefore, similar to the aerobic training alone, the combined training seems to be a good strategy to reduce the inflammatory and metabolic dysfunctions of T2DM.

MetS

MetS patients underwent 30 weeks of combined training (30 to 45 min of moderate to relatively fast speed walk (measured by rating of perceived exertion) plus 3 sets of 10 repetitions at 70 % 1RM) and purinergic activity of lymphocytes was evaluated [103]. After training, the lymphocytes of patients with Mets showed a reduction in the hydrolysis of ATP, ADP and an increase in the activity of the enzyme adenosine deaminase, reaching similarity with the control group. These findings suggest anti-inflammatory activity of lymphocytes, since the adenosine molecules (regulated by adenosine deaminase) promote suppression on the proliferation of T cells and the secretion of pro-inflammatory cytokines [104, 105]. On the other hand, after 12 weeks of HIIT (4 × 4-min at 90 % HRmax with 3 min active recovery at 70 % HRmax between intervals) there were no changes in the gene expression of TNF-α, p65 NF-kB, IL-6 and IL- 10 in PBMCs of women with MetS [106]. However, the training protocol decreased circulating concentrations of glucose, leptin, resistin, ghrelin, TNF-α, IL-6, IL-18 and INF-γ and increased of IL -10 and adiponectin, curiously, without reduction of body fat [106] . These findings suggest the need for detailed evaluations of the subpopulations of cells that compose PBMCs, as well as the possible participation of resident immune cells, macrophages for example, on secretion of cytokines in patients with MetS. In summary, it seems that combined training is a promising strategy to optimize the regulation of inflammatory response of lymphocytes.

Monocytes and lymphocytes physical exercise-induced morpho-functional changes in metabolic diseases

Metabolic diseases originate from multifactorial processes, such as external factors (sedentary lifestyle, unhealthy eating and tobacco) [107, 108] and internal factors (genetics, polymorphisms, in-

efficiency of proteins and enzymes) [109, 110]. Integrating these multifactorial manifestations has not been an easy task, due to unclear mechanisms of mediation of signaling pathways. However, the influence of behavioral aspects such as sedentary behavior and poor dietary intake on the development of metabolic diseases is well discussed. Thus, mechanisms based on local inflammation of the gastrointestinal tract [111, 112] or adipose tissue [113] have been proposed as protagonists in the development of systemic inflammation associated with metabolic diseases (▶ **Fig. 1**).

It is recommended that individuals with obesity should exercise for at least 250 min/week at a moderate-to-vigorous intensity, spread over 3–5 days and achieve a total weekly energy expenditure > 1500 kcal [114, 115]. Obese individuals should to prioritize whole-body aerobic exercises (e. g., walking, rowing, stepping) and be complemented by resistance exercises (2–3 days/week at 60–70 % of 1RM) [114, 115]. In addition to being offering structured exercise interventions, individuals with obesity should also be stimulated to increase their daily life physical activity level (e. g., taking the stairs, walk or cycle more often to cover smaller distances, etc.) and to reduce the hours spent sitting [114–116]. Increasing habitual physical activity levels and participation in structured exercise training is considered as a class 1 A intervention in the treatment of obesity [114–116]. Interestingly, a limited number of studies which evaluates the daily life physical activity level of obese participants.

A recent study published by Verboven and Hansen [117], critically demonstrates that the assumption that physical exercise will lead to a substantial decrease in adipose tissue mass in obese individuals no longer contributes to current observations in clinical practice. In contrast, physical exercise should be a powerful tool to target cardiometabolic risk, physical fitness, and quality of life. In agreement with the statement of Verboven and Hansen, previous studies from our research group and colleagues have demonstrated that both intensity and duration of physical exercise seem to be determinant to establish an anti-inflammatory environment, improving cardiometabolic health, polarization of macrophages (M2), and expansion of Tregs and Th2 lymphocytes [8, 20, 24, 27–30,

118–120] – which is more comprehensively elucidated in health, aging and metabolic diseases (see review Padilha et al. [120]; Cabral-Santos et al. [29, 118]). Here we propose highlighting the potential mechanisms involved in morpho-functional changes in monocytes, lymphocytes and PBMCs induced by different intensities and types of physical exercise in metabolic diseases.

HIIT is well-known to be time-efficient, a session is consisted by maximal effort and higher energy expenditure [121]. Previous studies have demonstrated the higher the intensity the greater is adrenergic discharge (catecholamines) [31, 40] and metabolic stress [32, 122]. The sympathetic nervous system controls diverse biological processes such as heart rate and blood flow, and major responsible for the ''fight or flight'' response that is provoked by acute stress. Most tissues, such as, lymph nodes, adipose tissue and skeletal muscle are innervated by sympathetic nervous system fibers and highly diverse cell types respond to sympathetic nervous system neurotransmitters through cell surface G protein-coupled α- or β-adrenergic receptors (ARs) [123]. Stress-induced activation of the sympathetic nervous system influences the activity of enzymes and proteins, as well as immune responses [124]. During acute high and moderate intensity exercise, there is an increase the glucose uptake by translocating the glucose transporter- 4 (GLUT-4) in skeletal muscle [125] and increase of IL-10 secretion stimulated of LPS [30]. Acute adrenoceptor stimulated by physical exercise activates the cholinergic anti-inflammatory pathway [126]; the autonomic nervous system interacts with the immune system modulating the inflammatory process [127]. Neural-immune interaction is known as cholinergic anti-inflammatory pathway, an endogenous, physiological mechanism by which acetylcholine from the valgus nerve, via the α7 sub-unit of the nicotinic acetylcholine receptor (α 7nAChR), interacts with the innate immune system to modulate and restrain the inflammatory cascade [127, 128]. Specifically, acetylcholine, the main vagal neurotransmitter, attenuates the release of pro-inflammatory cytokines TNF-α, IL-1β, IL-6 and IL-8, but not the anti-inflammatory cytokine IL-10 [127].

In immune cells, β2 adrenergic signaling stimulates the preferential mobilization of inflammatory phenotypes, such as CD16+ monocytes and CD8+ T-cells into the bloodstream after physical exercise session [103]. These cells, especially senescent T cells, are mobilized to the peripheral tissues and undergo apoptotic stimuli, stimulating the creation of an "vacant space" where new cells will be matured and replaced in the circulation [104]. Thus, the vacant space theory contributes to the reduction in inflammatory lymphocytes in inflammation associated with metabolic diseases. The practice of physical exercise stimulates redistribution in the proportion of these cells in the long-term.

In addition to the increase in catecholamines during physical exercise, the contraction of skeletal muscle stimulates a low and transient increase in myokines, such as IL-6, during each exercise session [105]. This scenario results in upregulation of anti-inflammatory cytokines (IL-10 and IL-1ra), leading to the increase in regulatory immune cells that manage the inflammation resolution [105, 106]. The anti-inflammatory and catabolic environment provided by the physical exercise sessions modulates signaling pathways of energetic sensors, such as AMPK and mTOR in monocytes and lymphocytes, leading to metabolic reprogramming with predominance of oxidative phosphorylation [94]. In fact, the increase
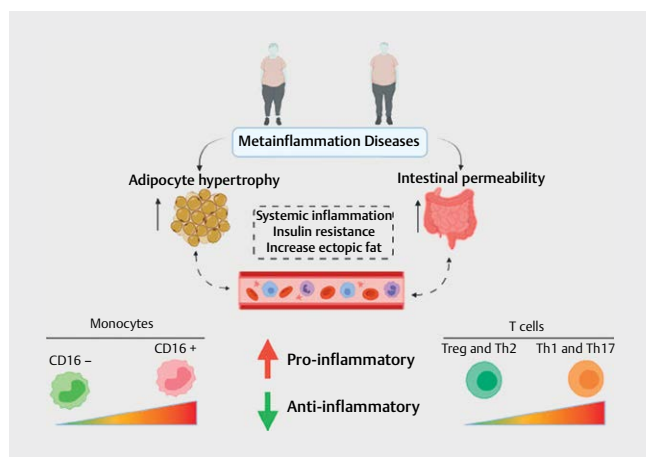
▶ **Fig. 1** Meta-inflammation diseases-induced systemic inflammation events on morpho-function changes of monocytes and T cells. Created with BioRender.com [rerif].
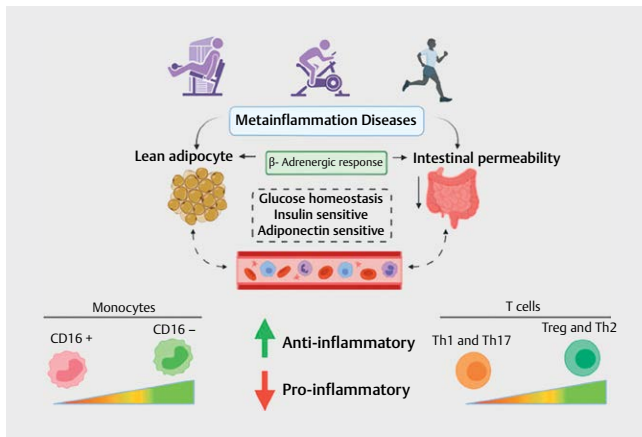
▶ **Fig. 2** Different type and intensities as key variable of physical exercise on morpho-function changes of monocytes and T cells in individuals with metainflammation diseases. Created with BioRender.com [rerif].

▶ **Fig. 3** Summary events-induced acute and chronic physical exercise on changes of monocytes and T cells in individuals with metainflammation diseases. Created with BioRender.com [rerif].
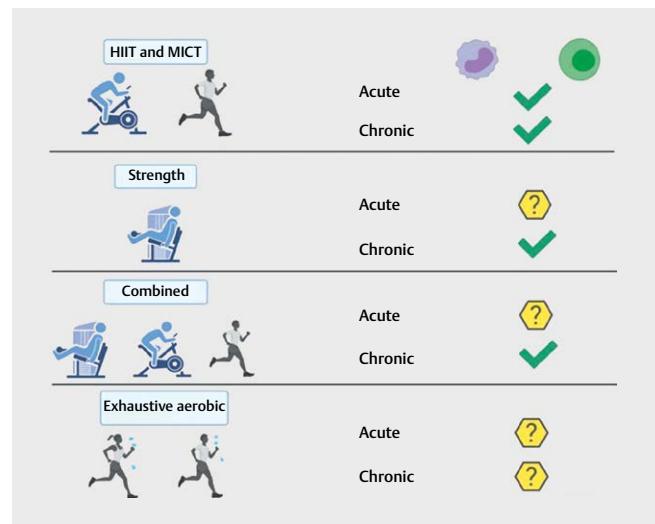
in the oxidative pathway for ATP resynthesis is necessary for the anti-inflammatory characteristics of monocytes and lymphocytes [94, 107], therefore, this mechanism is promising for the inflammatory control in metabolic diseases.

Together, the increase in catecholamine concentration, the transient increase in anti-inflammatory cytokines, and the regulation of energy substrates during physical exercise sessions can be crucial for the increase in regulatory monocytes and lymphocytes and control of inflammation associated with metabolic diseases (▶ **Fig. 2**). It is worth mentioning that all types of physical exercise presented in this review were good anti-inflammatory strategies, however, low intensities may not provide sufficient stimulus. Additionally, exhaustive exercise, especially aerobic, should be prescribed with caution when aiming at an anti-inflammatory environment.

Future perspectives and conclusion

This perspective review highlighted the intensity and type of physical exercise as a potential determinant of changes in monocyte and lymphocyte phenotypes in individuals with metabolic diseases. In relation to the aerobic exercise acute session, except for exhaustive practice, HIIE and moderate intensity continuous exercise are good anti-inflammatory strategies. Although strength exercise is an important tool for musculoskeletal, metabolic, and cardiovascular adaptations, future studies should evaluate the contribution of a single session, isolated or combined with aerobic exercise, on the modulation of monocytes and lymphocytes of individuals with metabolic diseases. In the long term, HIIT, MICT, strength, and combined training protocols are effective in providing anti-inflammatory adaptations. It is worth mentioning that, even though many patients with metabolic diseases have difficulty in performing certain physical exercises, the progression of intensity to at least moderate levels should be encouraged, in order to provide better immunological adaptations.

Finally, from an immunological point of view, we strengthen the wide variety of training protocols available to negatively regulate the inflammatory environment in individuals with metabolic dis-

eases. The variety of possibilities could favor adherence to training and, consequently, contribute to treatment (▶ **Fig. 3**).

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Conflict of Interest

The authors declare that they have no conflict of interest.

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