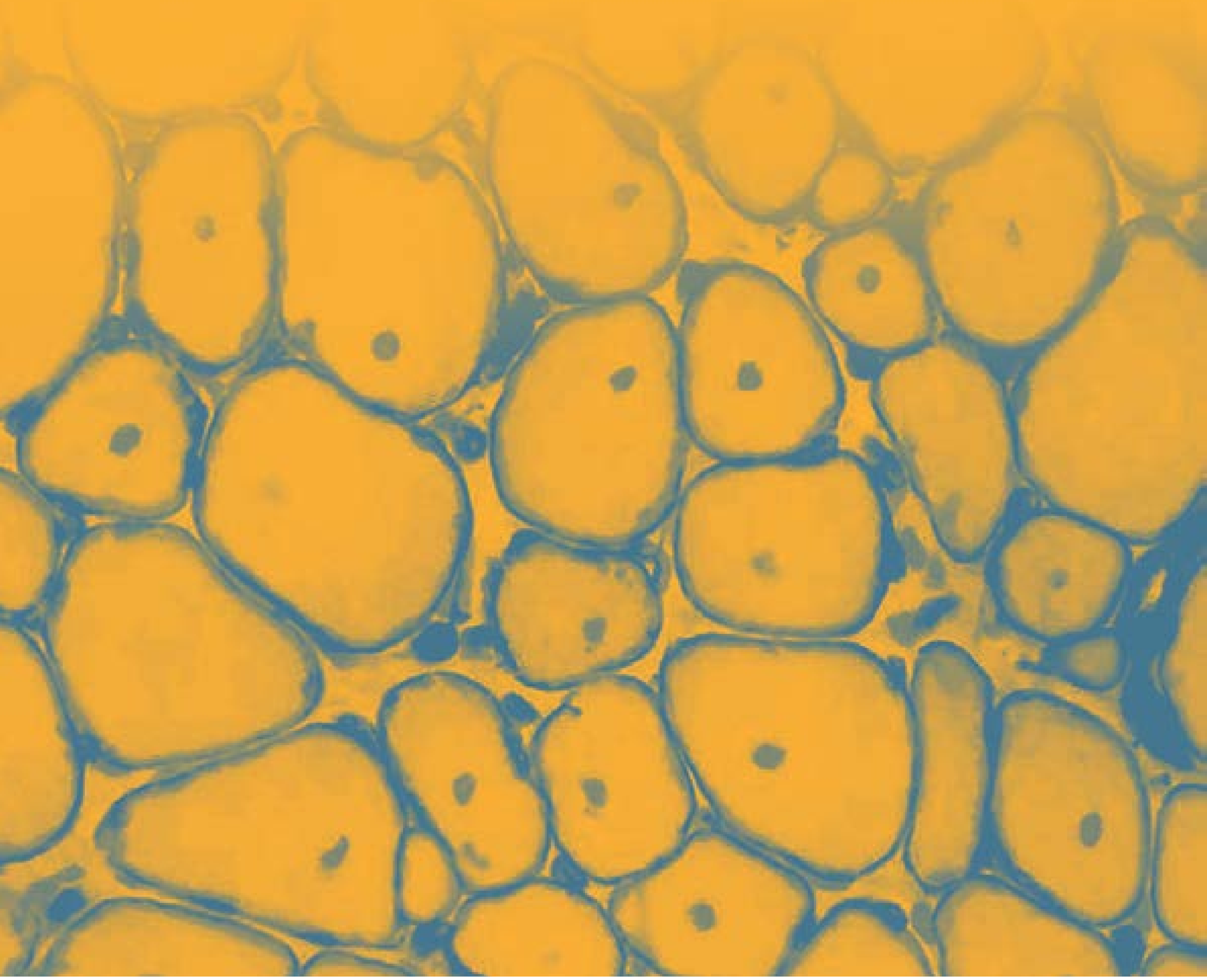
Physiological Mini Reviews

14

Volume



Vol. 14, May-June, 2021
ISSN 1669-5410 (Online)
pmr.safisiol.org.ar

Physiological Mini Reviews

SAFIS
Sociedad Argentina de Fisiología

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Sección de Fisiología de la Sociedad Uruguaya de Biociencias (SUB)

Physiological Mini-Reviews

[ISSN 1669-5410 (Online)]

Edited by **the Argentinean Physiological Society and the Latin American Association of Physiological Sciences**

Journal address: Centro de Investigaciones Cardiovasculares y Cátedra de Fisiología y Física Biológica.
Facultad de Ciencias Médicas; Universidad Nacional de La Plata;
La Plata, Buenos Aires, Argentina. Tel.-Fax: +54-211-4834833
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PHYSIOLOGICAL RELEVANCE OF AEROBIC EXERCISE TRAINING FOR THE PREPARATION OF BARIATRIC SURGERY CANDIDATES

Sergio F Martinez-Huenchullan[1,2,3], Mariana Kalazich-Rosales[4], Camila Mautner-Molina[4,5], Francisca Fuentes Leal[4], Carlos Cárcamo-Ibaceta[4,6], Charmaine S Tam[7], Pamela Ehrenfeld[3,8]

[1] Unidad de Kinesiología, Instituto de Aparato Locomotor y Rehabilitación, Facultad de Medicina, Universidad Austral de Chile, Valdivia, Chile.
[2] Laboratorio de función cardiorrespiratoria y metabólica – Neyün, Facultad de Medicina, Universidad Austral de Chile, Valdivia, Chile.
[3] Centro Interdisciplinario de Estudios del Sistema Nervioso (CISNe)
[4] Clínica Alemana Valdivia, Valdivia, Chile
[5] Escuela de Kinesiología, Universidad San Sebastián, Valdivia, Chile
[6] Instituto de Cirugía, Facultad de Medicina, Universidad Austral de Chile, Valdivia, Chile
[7] Northern Clinical School, University of Sydney, Sydney, Australia.
[8] Laboratorio de Patología Celular. Instituto de Anatomía, Histología y Patología, Facultad de Medicina, Universidad Austral de Chile, Valdivia, Chile.

Correspondence to: sergio.martinez@uach.cl

ABSTRACT

Bariatric surgery is popular among clinicians to treat obesity because of its high impact on body weight reduction. However, the fast rate of weight loss has several consequences, such as loss of muscle mass and strength, and functional capacity. Therefore, preoperative interventions are needed to secure the surgery's success, where physical exercise could be an effective intervention. Nevertheless, the most effective preoperative exercise prescription, along with its potential post-surgical carry-over effects, is still unclear. Recent studies have highlighted that exercise programs that differ, for instance, in intensity, induce differential metabolic benefits, that seem to be tissue-specific. This might be clinically relevant since it has been described that obesity-related metabolic impairments are not stereotypical in humans. This brief review analyses some tissue-specific disturbances derived from obesity, and how aerobic exercise programs, particularly high-intensity interval training and moderate-intensity constant training could elicit differential benefits, particularly in candidates to undergo bariatric surgery.
Keywords: Exercise, bariatric surgery, high-intensity interval training, overweight

RESUMEN

La cirugía bariátrica es popular para el tratamiento de la obesidad debido a su alto impacto sobre la reducción del peso corporal. Sin embargo, esta acelerada pérdida de peso tiene variadas consecuencias, tales como el descenso de masa y fuerza muscular, así como de la capacidad funcional. Por tanto, el manejo preoperatorio es necesario para asegurar el éxito quirúrgico, dentro de las cuales el ejercicio físico ocupa un lugar importante. No obstante, se desconoce la prescripción del ejercicio más efectiva en esta población, así como los potenciales efectos que puedan perdurar posterior a la cirugía. Estudios recientes destacan que programas de ejercicio que difieren, por ejemplo, en intensidad, inducen beneficios metabólicos diferenciales, los cuales parecer ser tejido-dependientes. Esto puede ser clínicamente relevante, considerando que las alteraciones metabólicas asociadas a obesidad no son estereotípicas en humanos. Esta breve revisión analiza algunas alteraciones derivadas de obesidad, las cuales se presentan de forma específica en diferentes tejidos, y además como diferentes programas de ejercicio aeróbico, tales como el interválico de alta intensidad como el de intensidad moderada y constante podrían provocar beneficios diferenciales, particularmente en candidatos a cirugía bariátrica.
Palabras clave: ejercicio, cirugía bariátrica, entrenamiento interválico de alta intensidad, sobrepeso.

Received: August 23rd, 2021. Accepted in the final form: September 27, 2021

Obesity and bariatric surgery

Obesity is a global health problem, which its prevalence has steadily increase in the last decades, where it has been reported that around one-third of the world population is classified as overweight or obese [1]. As a consequence of obesity, several impairments have been described involving the cardiovascular, metabolic, respiratory, and cognitive systems, making it a key public health challenge in the present and near-future [2]. Therefore, lifestyle modifications such as changes in diet and increases in physical activity levels are highly recommended in the management of obesity. However, and considering the multifactorial nature of obesity, these interventions on their own are not enough for successful body weight loss and restoration of metabolic health [3].

Because of these previous considerations, bariatric surgeries have gained popularity among health professionals in the management of severe obesity (body mass index (BMI) ≥ 35kg/m^2 [4]. This surgery aims to reduce the stomach space, so with the consequent decrease in food intake, rapid weight loss is achieved. Interestingly, the number of performed bariatric surgeries has steadily increased in the last decades. Paolino et al, after collecting data from 61 countries, described that the number of bariatric surgeries showed a 3.6-fold increase in the period from 2003 to 2016 [5]. Its low mortality levels (0.32%) [6] make it a very safe procedure with postoperative complications in the range of 0 to 10.6% [6], and highly effective in normalizing body weight and overall metabolism outcomes [7]. However, considering the abrupt change in energy intake, pre- and post-operative interventions are included in the candidate to undergo bariatric surgery management, being the supervised physical exercise one of the most frequent.

Interestingly, most of the literature on the matter is focused on exercise prescription during the post-operative period. A recently published systematic review and meta-analysis gathered the information of 20 studies on the issue. The main findings were that exercise during the post-operative period was successful in optimizing body weight loss, fat mass loss, and improving physical fitness [8]. As a response to these findings, consensus from several scientific societies has been written proposing directions in terms of how exercise should be prescribed during the pre- and postoperative period [9, 10]. However, the recommendations for the pre-operative period are unspecific, regarding if aerobic exercise is suggested. This is without question a reflection of the lack of studies exploring the potential benefits that pre-operative interventions, particularly in the form of programmed exercise could confer [11], spite of the well-known metabolic benefits of exercise in people with obesity and diabetes [12]. However, a feature that complexes the understanding of the mechanisms behind obesity-related impairments, is the affection of the metabolic function of different tissues, in a non-stereotypical manner [13].

For instance, adipose tissue is known to play an important role as an endocrine organ, and adiponectin is described as one of the most abundant adipokine in the circulation [14]. Adiponectin also has autocrine/paracrine actions in adipose tissue, where its high-molecular-weight (HMW) isoform has been described as the most bioactive complex [15]. During obesity, lower levels of HMW adiponectin along with decreased activity/quantity of its most abundant receptor, adiponectin-receptor 1 (ADIPOR1), are claimed to partially mediate the development of insulin resistance by several mechanisms [16]. Adiponectin can activate 5' adenosine monophosphate-activated protein kinase (AMPK) by increasing the pAMPK/AMPK ratio, which promotes glucose transporter type 4 (GLUT4) vesicle formation and translocation to the adipocyte's membrane. Therefore, an anti-hyperglycemic feature has been attributed to this hormone [17], the same that during obesity is impaired [16]. This review is primarily focused on adiponectin, however, other adipokines that have raised scientific attention in the latest years are leptin, resistin, apelin, and visfatin, which regulates several physiological processes, such as food intake, insulin resistance, and inflammation, cardiovascular homeostasis, and beta-cell function respectively. Interestingly, dysregulations from all of these proteins have been described in an obesity context, changes that make the subject susceptible to develop low-grade systemic inflammation and insulin resistance [18]. In terms of mitochondrial function, adipocytes produce >95% of their ATP through oxidative phosphorylation [19], energy that is mainly used for triglyceride synthesis and adipokine release. During obesity, impairments on these processes have been described [20], nevertheless one feature of the adipocyte metabolic function has been extensively studied in recent years, which is the futile utilization of energy, a process known as mitochondrial uncoupling. Here, the energy derived from the proton motion dissipation that is normally used to produce ATP in the mitochondria is released in the form of heat. Proteins associated with uncoupling are Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) and uncoupling protein 1 (UCP1, mainly present in brown adipocytes) [21]. However, under certain circumstances, white adipose tissue can exhibit brown areas (i.e. browning) where the presence of these mitochondrial proteins is particularly high. Exercise has been described as an intervention that could induce browning in adipose tissue, where key proteins described in this process are irisin and PGC-1α [22]. The metabolic benefits derived from this adaptation are intriguing, given that weight loss, reduce adiposity, increased energy expenditure, and increased of insulin sensitivity has been described as consequences of higher levels of beige adipose tissue [23]; nevertheless, these results have been primarily described in rodents, whereas, in clinical trials, the results are inconclusive [24]. Interestingly, in animal models of obesity, it has been described that the content of browning-related proteins is decreased [25, 26], suggesting that obesity disrupts this feature, further predisposing this tissue to continue its expansion rather than its dissipation.

Another common consequence of obesity is the development of non-alcoholic fatty liver disease (NAFLD). This complication is particularly relevant when studying obesity-derived metabolic disease, given that it has been described as one of the sources for the development and maintenance of systemic insulin resistance, where chronic hyperglycemia and hyperinsulinemia are described as the main promoters of this condition [27]. Moreover, if this excessive fat accumulation is chronic, liver damage and dysfunction can be developed through several mechanisms, including inflammation and fibrosis, characterized by increases in growth factors such as transforming growth factor β (TGFβ) and collagen [28, 29]. Furthermore, impairments in liver glucose metabolism can be observed during obesity, given that decreases in pAMPK/AMPK ratios along with lower levels of mitochondrial proteins (e.g.: peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α)) have been described in mice and humans [30, 31], changes that overall impair glucose metabolism and promotes hyperglycaemic states.

Skeletal muscles are described as the main glucose disposal organs in the human body. Therefore, impairments in its biology are highly linked with the development of insulin resistance. Recently, it has been described that skeletal muscle produces adiponectin, which acts in an autocrine/paracrine manner [32]. It has been proposed that, during obesity, this response becomes dysfunctional given that quadriceps from high-fat-fed mice have shown lower levels of HMW adiponectin and ADIPOR1 [32]. These impairments have been associated with decreases in AMPK activation pathways which in turn reduces GLUT4 vesicles formation and translocation impairing glucose uptake and metabolism [33]. On the other hand, exercise has shown adiponectin related effects in skeletal muscle, given by increases in mitochondrial proteins (e.g., PGC-1α), which are associated with increases in aerobic capacity [34], therefore, obesity-related decreases of these mediators have been associated, in part, with skeletal muscle adiponectin disturbances [32].

As an integration of all these disturbances, plasma/serum proteomic studies have become an useful tool to gather a global view of the metabolic impairments related to obesity resulting in an efficient and feasible method [35]. In this context, clinical and preclinical studies have agreed that obesity derives in a disrupted circulating proteome, characterized by an increase in systemic inflammation mediators [36] and lipid transport proteins, such as apolipoprotein A1 [37]. Similarly, in a recent study from our group, we observed that after 10 and 20 weeks of high-fat feeding, plasma proteome from C57BL/6 mice showed significant increases of apolipoprotein E, apolipoprotein C-II, and fructose-biphosphate aldolase B (ALDOB) [38], proteins again related with lipid transport and liver damage.

To summarize the interaction of the metabolic impairments derived from obesity, figure 1 illustrates the described effects of obesity on insulin-sensitive tissues and plasma proteome (e.g., inflammatory mediators and hepato-adipo-myokines).

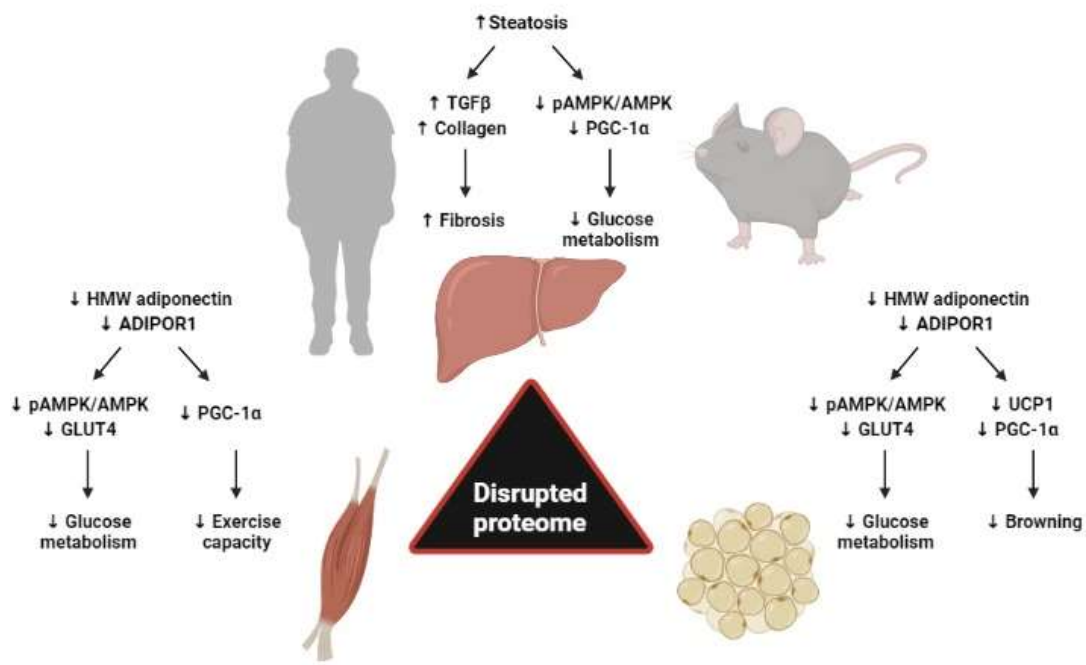

Figure 1. A summary of obesity-related metabolic impairments described by us [38-41] and others [16, 20, 25, 28, 30, 31, 33, 36, 37] in insulin-sensitive tissues and plasma proteome from clinical and preclinical studies. Abbreviations: TGFβ: transforming growth factor-beta; pAMPK: phosphorylated AMP-activated protein kinase; AMPK: AMP-activated protein kinase; PGC-1α: peroxisome proliferator-activated receptor gamma coactivator 1-alpha; HMW: high-molecular weight; ADIPOR1: adiponectin receptor 1; GLUT4: glucose transporter type 4; UCP1: uncoupling protein 1. Figure created in BioRender.com

Exercise in bariatric surgery candidates

In terms of physical exercise, it has different characteristics that are known to exert differential physiological adaptations. For instance, exercise can be prescribed with a particular modality, frequency, duration, and intensity, where the relevance of the latter has been thoroughly described [42], given that vigorous exercises (where a limited number of repetitions can be performed) activate anaerobic pathways to extract energy by skeletal muscles, which are mainly dependent on glycolysis; whereas exercise at which the intensity allows the person to sustain the effort for several minutes activates pathways dependent on nutrient oxidation in the mainly form of carbohydrates and lipids [43]. Considering the previous, aerobic exercise is frequently described in the context of obesity, specifically for its positive effects on glucose transport and insulin sensitivity in normal and pathological conditions (i.e. type 2 diabetes). Kieran et al. described decreases in fasting insulin levels and higher levels of insulin sensitivity and glucose disposal rates with only 7 days of running/cycling exercise in adults with obesity and type 2 diabetes [44].

Considering the clear benefits of performing exercise in an obesity context, a barrier that the clinician has to face during the management of candidates to undergo bariatric surgery are the very low levels of spontaneous physical activity that they describe, which are reported as low as that only a 10% of them performed the recommended levels of physical activity [45], the factor that predisposed them to present lower cardiorespiratory fitness levels, which in turn is associated with longer operating room times and Intensive Care Unit days [46]. On top of this, the recommended physical activity levels for these patients are higher than the ones recommended for the global population (150 min/week) [42], where for candidates to undergo bariatric surgery 200 min/week were required to observe higher levels of weight loss post-surgery [47]. These findings take higher relevancy considering that medically supervised weight loss programs (without exercise) during the preoperative period have shown little to no effect on this outcome [48]. Because of these barriers, recent efforts have been focused on finding new exercise modalities to ensure adherence during the pre-operative period.

As a response to the classical moderate-intensity continuous exercise (MICT), high-intensity interval training (HIIT) has been proposed and developed more intensely during the last two decades [49]. The reported advantages of HIIT are to be more enjoyable and time-efficient than more classical exercise prescriptions, such as MICT [50]. Moreover, some authors have suggested that HIIT confer higher physiological adaptations than MICT [49], even under an obesity context. However, recent studies have questioned this statement. This is the case of the study of Jung et al. where after two weeks of MICT and HIIT, adults with prediabetes showed similar improvements in cardiorespiratory fitness and systolic blood pressure [49]. To complement these findings recent studies and systematic reviews/meta-analyses have found comparable results in people with obesity in terms of aerobic capacity, body weight loss, total fat mass, and cholesterol [51, 52]. Moreover, Keating et al. reported that in terms of fat distribution, MICT exhibits better results reducing the android fat percentage in overweight adults compared to HIIT [53], highlighting that depending on the outcome studies, exercise intensity might have a specific effect.

No studies comparing MICT vs. HIIT in candidates to undergo bariatric surgery are known. However, studies describing combined exercise training (aerobic + anaerobic) [54-57] or only strengthening exercises [58] are available. The aerobic component was always of moderate-intensity and, as expected, physiological outcomes such as aerobic capacity, and body fat mass improved after exercise training.

Even when the previously reported results are promising, their findings are sustained mainly by clinical/physiological measurements, where systemic (e.g., fasting glucose, insulin, oral tolerance glucose test, lipid profile), and specific metabolic outcomes (e.g., tissue markers of insulin action and glucose transport) are hugely lacking. This is particularly concerning knowing that obesity-related insulin resistance is far to be a stereotypical process, since variations in its presentation are described and seems to be independent of body weight and fat mass among individuals with obesity [13]. These results might find an explanation in that obesity-associated insulin resistance is a process that depends on the function of several organs that are known to be insulin-sensitive (e.g. skeletal muscle, white adipose tissue, and liver). This point is particularly relevant during bariatric surgery considering that some patients exhibit certain resistance to this procedure, a phenomenon that is defined as the lack of metabolic health improvements after the surgery [59], where the metabolic/endocrine function of insulin-sensitive tissues is proposed as the main etiology of this phenomenon.

Studies that have explored these exercise regimes and tissue-specific metabolic effects of exercise during obesity are scarce and have been mainly done in animal models. However, these studies have reported after comparing MICT vs HIIT seems to be tissue-dependent. For instance, 10 weeks of HIIT showed improvements in body insulin sensitivity, increases in the glucose transport protein GLUT4 in the gastrocnemius muscle of db/db mice, changes not seen after MICT [60]. In complement, even when similar liver insulin-sensitizing effects from MICT and HIIT have been described in diet-induced obese rats, the latter reduced inflammatory mediators such as NF-κB [61], and in white adipose tissue improvement in insulin signaling have been described in high-fat-fed mice [26]. Considering these results, HIIT seems to be metabolically preferable over MICT during obesity in terms of metabolic benefits; however, limitations in terms of exercise prescription in the previous studies hinders the possibility of making fair comparisons between HIIT and MICT, given that differences in exercise intensities are usually normalized by exercise volume [26] instead of equalizing intensities between programs. This is relevant because when HIIT and MICT are similar in terms of energy expenditure the systemic metabolic effects on humans with overweight or obesity tends to be comparable in terms of decreases in intrahepatic fat levels and circulating insulin [62]. In this context, in previous experiments from our group, we have shown tissue-specific effects of HIIT and MICT on high-fat-fed mice [39], where the average intensities, session duration, and distance covered per session were comparable between training programs. For instance, we observed that HIIT preferably induces changes in white adipose tissue depots, such as increases in UCP-1 protein levels, whereas MICT regimes induce liver-specific benefits, such as decreases in protein levels collagen 1 and mRNA levels of transforming growth factor-beta 1 (Tgf-b1), collagen 1a1 (Col1a1), and interferon-gamma-induced protein 10 (Cxcl10) [39]. Moreover, these differences between training programs were also seen in the heart, where MICT, but not HIIT, was able to impede the HFD-driven reduction of the high-molecular-weight adiponectin isoform [63], which has been described as the most bioactive. As a reflection of these tissue-specific benefits from one exercise program over the other, when the plasma proteomic profile of high-fat-fed mice trained with HIIT or MICT is compared, differences can also be found, where MICT has been described as more effective in normalizing obesity-related disturbances at this level [38]. Thus, seems that the exercise intensity, even when the training volume and average intensity are similar, evokes differential metabolic benefits in the context of obesity (Figure 2).

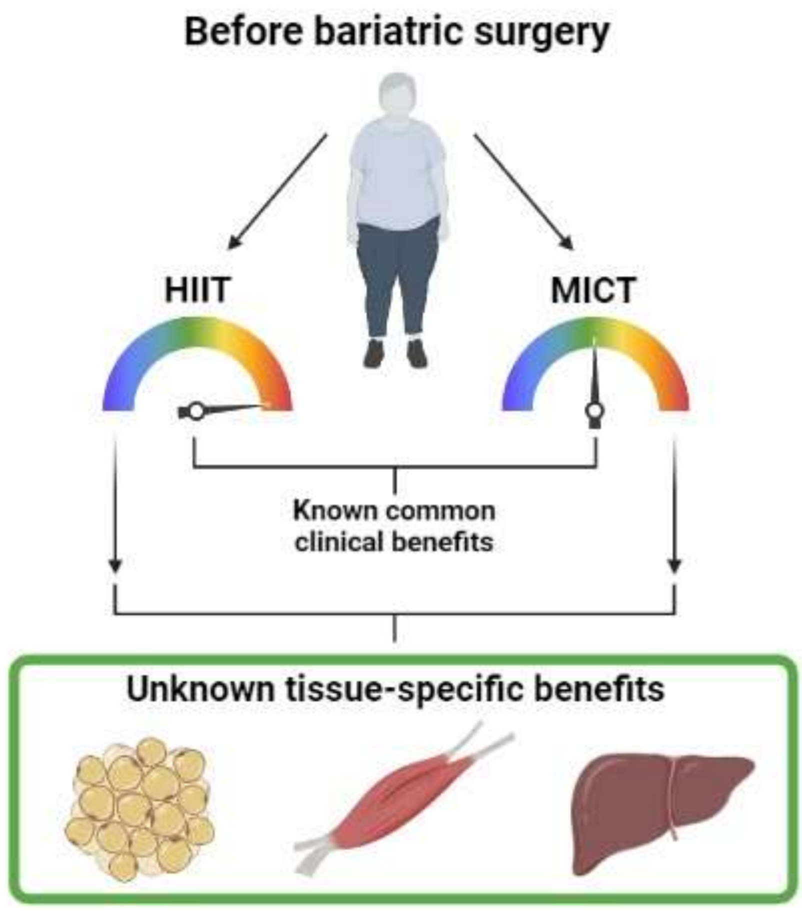

Figure 2. Exercise intensity in candidates to undergo bariatric surgery. Both HIIT and MICT are known to induce common clinical benefits, such as normalization of fasting glucose and increases in systemic insulin sensitivity. However, its possible tissue-specific benefits are, to date, unclear. Abbreviations: HIIT: high-intensity interval training; MICT: moderate-intensity constant training. Figure created in BioRender.com

Final comment

The previously described findings drive us to hypothesize that aerobic exercise intensity confers specific effects on insulin-sensitive tissues during obesity; however, clinical studies aimed to corroborate these findings are scarce, and more importantly, no studies on candidates to undergo bariatric surgery are known to investigate if there is a specific type of exercise program that exerts the most beneficial metabolic effects on this population. In complement and considering the relevance of the maintenance of metabolic benefits post-surgery on these patients, no studies have compared if the metabolic effects of HIIT or MICT during the preoperative period are preserved (or augmented) during the post-surgery period. Thus, considering the multiple metabolic disturbances derived from obesity, such as insulin resistance and low exercise tolerance, we hypothesize that aerobic exercise (e.g. HIIT and MICT) is particularly adequate to counter them, given its benefits on insulin-sensitive tissues' metabolic function. Other forms of exercise, such as resistance training, which are primarily focused on increasing skeletal muscle mass and function, could enhance the benefits from aerobic exercise in candidates to undergo bariatric surgery, considering that skeletal muscles are major glucose storage tissues. However, future clinical trials should address these questions by comparing the effects of specific exercise programs on the metabolic disturbances observed in these patients.

FUNDING DETAILS

SM-H is supported by the National Agency of Research and Development (ANID) through an Early Career Research Grant (FONDECYT de iniciación en investigación), code 11200391. PE is supported by the National Agency of Research and Development (ANID) through a Research Grant (FONDECYT regular), code 1201635.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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ABOUT AUTHORS

Dr. Sergio F Martínez-Huenchullán is an Assistant Professor and Head of the Cardiorespiratory and Metabolic Function Laboratory – Neyün at the Faculty of Medicine of Universidad Austral de Chile. Sergio's current research interests are focused on the effects of different exercise prescriptions on the physical and metabolic function in an obesity context, combining clinical and basic science tools to understand the differential mechanisms by which specific exercise programs exert their metabolic benefits.

Lic. Mariana Kalazich-Rosales is a Physical Therapist at Clinica Alemana Valdivia and member of the Chilean Society of Bariatric and Metabolic Surgery. She specializes in the rehabilitation of people with cardiovascular and metabolic dysfunctions, such as candidates to undergo bariatric surgery.

Mg. Camila Mautner-Molina is a Physical Therapist and Head of the Physical Therapist team at Clinica Alemana Valdivia and Lecturer at Universidad San Sebastian. She holds a master's degree in Cardiorespiratory Physical Therapy and is a member of the Chilean Society of Bariatric and Metabolic Surgery. She specializes in the rehabilitation of people with cardiovascular and metabolic dysfunctions, such as candidates to undergo bariatric surgery.

Lic. Francisca Fuentes-Leal is a nutritionist and member of the Bariatric Patient Management Team of Clinical Alemana Valdivia. She specializes in the nutritional management of people with obesity, and her current research interest is related to the prevention, treatment, and management of obesity.

Dr. Carlos Cárcamo-Ibaceta is Associate Professor and Director of the Surgery Institute at the Faculty of Medicine of Universidad Austral de Chile. He is also surgeon of the Bariatric Patient Management Team at Clinical Alemana Valdivia and member of the Chilean Society of Bariatric and Metabolic Surgery.

Dr. Charmaine S Tam is a Senior Research Fellow at Northern Clinical School, University of Sydney and Program Manager in Clinical Analytics at Northern Sydney Local Health District, NSW, Australia. Charmaine works at the much-needed interface between health domain experts and data engineers and scientists, ensuring that insights from the burgeoning amount of digital health data are best utilized to lead to improvements in human health within appropriate governance and privacy safeguards. On a day-to-day basis, she manages an analytics team which focuses on harnessing insights from structured and unstructured data, such as free-text and images, extracted from eMR systems.

Dr. Pamela Ehrenfeld-Slater is a Full Professor, Head of the Laboratory of Cellular Pathology at the Institute of Anatomy, Histology, and Pathology in the Universidad Austral de Chile, with vast experience and productivity in the molecular and cellular biology of cancer, inflammation, and metabolism.