Exercising for Metabolic Control: Is Timing Important?

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Key Words

Aerobic exercise • Postprandial lipemia • Postprandial glycemia • Type 2 diabetes • Cardiovascular disease

Abstract

Atherosclerosis-related cardiovascular disease and diabetes mellitus are leading causes of mortality in the world and both disorders are closely related to the postprandial phenomena. Regular exercise is being strongly advocated as a precious tool in easing the global burden of chronic disease. Although exercise intensity, duration and frequency are well established in current guidelines for healthy and diabetic individuals, there is still no consensus on the optimal timing of exercise in relation to the last meal. The present paper reviews the existing literature on the 'when?' of aerobic exercise for metabolic control in healthy and diabetic individuals. Effective control of postprandial phenomena might prove to be a useful tool in the prevention of chronic disease. Exercise appears to influence glycemic and triglyceridemic responses differently depending on the meal composition and time lapse from meals. In healthy individuals, fasted-state exercise favors postprandial triglyceridemic control and the insulin sensitivity related to it. However, there is a lack of data on this matter in diabetic patients. On the other hand, when postprandial glycemia is of concern, aerobic exercise works better when performed after a meal, both in healthy and in diabetic patients.

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Introduction

Metabolism is highly influenced by energy turnover. Hence, the interplay between nutrition (the energy supplier) and exercise (the energy consumer) is particularly relevant to metabolic control in both the healthy and those affected by chronic disease.

Exercise, along with nutrition and pharmacologic agents, is recognized as a strong modulator of postprandial glycemic and triglyceridemic responses [1]. Nutritional, pharmacologic, and exercise interventions might be applied to the same individual simultaneously and, considering the fact that the glycemic and lipemic responses are time dependent, the net result of the three interventions could depend, at least in part, on the time sequence in which they are implemented. For this matter, the present paper will review the existing literature on the 'when?' of exercising for metabolic control, more specifically postprandial metabolic control, with a focus on glycemia and lipemia in healthy and in diabetic individuals. Only studies investigating the effect of aerobic exercise have been included, as this modality of exercise is the most standardized, thus allowing for between-study comparisons.

Exercise as a Prevention and Treatment Tool

The scientific world has begun to pay special attention to exercise, since a sedentary lifestyle is an important en-

vironmental risk factor for many noncommunicable illnesses. In fact, inactivity-related diseases are nowadays considered the leading causes of mortality in the world. Cardiovascular diseases, obesity, metabolic syndrome, type 2 diabetes mellitus (T2D), and associated complications cause a nonnegligible socioeconomic burden [2].

Therefore, exercise plays an exceptional role in the prevention and treatment of such conditions. Together with medical nutrition therapy and pharmacologic therapy, exercise therapy is one of the mainstays of diabetes treatment as recommended by the American Diabetes Association [3]. However, while diabetic patients seem to comply well with dietetic and pharmacologic interventions, their exercise levels remain low [4]. This might be partially due to the difficulty in prescribing exercise the same way as a pharmacologic agent. Indeed, there are many elements of exercise prescription that have not been clearly defined yet. There are some quantitative and qualitative aspects of exercise that should be considered when prescribing it. Research has mainly focused on the quantitative issue, i.e. the dose-response relationship of exercise and health outcomes. Generally, there is agreement on an inverse and linear relationship between aerobic exercise and the rates of all-cause mortality, the incidence of mortality from cardiovascular disease, and the incidence of T2D [5], although this might be subject to inter-individual variability [6]. Current guidelines recommend healthy adults accumulate at least 150 min per week of moderate-intensity or ≥ 75 min per week of vigorous-intensity aerobic exercise. Engaging in resistance exercise for an additional 2–3 days per week is recommended to further optimize the benefits of exercise [7]. Guidelines for diabetic patients are similar to the ones for healthy individuals [8].

While the scientific and medical communities have reached a consensus on the minimal dose of exercise, which certainly is the ‘heart’ of exercise prescription, there is still some detail missing in the ‘directions for use’ section. On a typical medical prescription, the ‘distance from meal’ would stand just beside the ‘frequency of use’ under the ‘directions for use’ section. However, we are lacking such indications regarding exercise.

Temporal optimization of exercise in relation to meal consumption might be important to further increase the benefits from the same amounts of exercise. This might prove particularly beneficial to patients who need to further improve health outcomes from exercise but cannot increase the intensity or duration of exercise beyond a certain limit.

Meal Consumption as a Metabolic Disrupter: Importance of Targeting Postprandial Phenomena

It is well known that the response to exercise is highly dependent on the nutrient availability provided by the food intake and on the related hormonal background. Meal consumption provokes a series of endocrine and paracrine time-dependent responses that vary with respect to meal volume and composition [9]. Some of these responses are then summed from one meal to the next. The 24-hour timeframe can thus be divided into two metabolically distinct periods: the postprandial period and the postabsorptive period [10]. While there is little variability of substrate concentrations in the postabsorptive state, there is an increase in glycemic and lipemic levels in response to a meal in the postprandial state. The transition from postabsorptive to postprandial involves a complex interplay of mechanisms that lead to a shift in substrate utilization, defining the so-called metabolic flexibility [11].

Postprandial events have long been acknowledged as risks for atherogenesis. Zilvermit [12] recognized atherosclerosis to be a postprandial phenomenon, referring mainly to postprandial lipoprotein remnants. The strong association between these two phenomena has been repeatedly confirmed ever since. A high-fat diet and a single high-fat meal have been accused of inducing functional derangements that lead the way to insulin resistance and T2D [13]. Diabetes, on the other hand, is an independent risk factor for atherosclerosis [14, 15]. Also, it has been extensively suggested that a better control of the postprandial triglyceridemia may help prevent chronic diseases. Indeed, Kishore et al. [16] demonstrated that, in T2D, acute lowering of free fatty-acid levels significantly improves hepatic and peripheral glucose effectiveness, i.e. the ability of hyperglycemia to inhibit endogenous glucose production. Hence, hyperlipidemia may be considered both as a risk factor for the development of and as a target for the prevention of chronic disease.

In addition to postprandial lipemia, postprandial hyperglycemia and glycemic peaks have been demonstrated to produce harmful byproducts and increase reactive oxygen species, which are nowadays retained as the most important common characteristic of chronic disease [17, 18]. Be it a cause or a consequence of diabetes, postprandial hyperglycemia has been identified as an important risk factor in the development of macro- and microvascular complications of diabetes through different possible mechanisms [17–24]. Accordingly, the IDF has identified postmeal glycemia as a target of diabetes treatment [24, 25]. The impression that might be created by the ex-

Table 1. Inclusion criteria for the reviewed studies

Study design	Experimental studies: -Randomized counterbalanced crossover -Parallel groups
Comparisons	Exercise vs. nonexercise Pre- vs. postexercise
Health conditions	Healthy T2D
Main outcome	Plasma glucose Plasma triacylglycerol
Exercise modality	Aerobic only (walking or cycling)
Exercise intervention	Single bout Training program

isting prevailing evidence is that only glycemia beyond the diabetic threshold level increases the risk of cardiovascular diseases. There is evidence, however, that the risk of cardiovascular events progressively increases with increasing of the so-called normal, nondiabetic glucose values [26].

It is now well established that chronic exposure to hyperglycemia (glucocentric approach) and hyperlipemia (lipocentric approach) can cause insulin resistance and T2D [27]. Diabetes, in turn, may result in failure to maintain normal postprandial and fasting values of the two, which then results in chronic complications. Hence, controlling postprandial hyperglycemia and hyperlipemia in healthy and diabetic individuals may result in a two-fold benefit. It may prevent diabetes and atherosclerosis-associated disorders in the healthy, while on the other hand in diabetic patients it may offer protection against diabetes progression and the development of its associated cardiovascular complications.

Exercise, with its effect on postprandial events, may be fundamental in interrupting the vicious cycle of chronic disease. Studies reviewed here point out that factors related to either exercise or meal characteristics, and the time interval between them, appear to importantly influence the effect of exercise.

Materials and Methods

To identify relevant reports on the effect of exercise on triglyceridemia and glycemia and the interaction with meal intake, a literature survey was carried out in PubMed (<http://www.ncbi.nlm.nih.gov/pubmed/>) and ScienceDirect ([\[direct.com/\]\(http://direct.com/\)\). The following filters were applied to the search: human studies, published in the last 20 years, English language. Aerobic exercise, postprandial glycemia, postprandial lipemia, time lapse from meal, pre- versus postmeal exercise, and diabetes were used as keywords. Additional relevant articles were identified from the reference lists of selected articles and from a hand search of pertinent journals.](http://www.science-</p></div><div data-bbox=)

Selected articles were further examined for eligibility. Only experimental studies, with a randomized, counterbalanced crossover design investigating the effect of either a single bout of aerobic exercise or a training program were included in the present review.

Inclusion criteria are presented in table 1.

Results

The relevant studies reviewed here are summarized in tables 2 and 3. Twenty-six studies were included in the final selection, 8 of which directly compared prior exercise with after-meal exercise [28–35]. The remaining 18 studies investigated the effect of exercise on postprandial events, modulating some parameters related to meals and exercise (i.e. exercise intensity and duration, meal size and composition) [36–53].

Aerobic Exercise and Postprandial Lipemia: Fasted versus Fed

Zhang et al. [35] compared the effects of 60 min of treadmill walking at 60% of the maximal oxygen consumption (VO_2max), performed either in the fasted state or after the consumption of high-fat meals. The authors concluded that exercising in the fasted state produces superior results with regard to postprandial plasmatic triglycerides (TG) and high-density lipoprotein (HDL) cholesterol concentrations. Particularly, the same exercise session performed the evening before a meal seemed to provide better overall postprandial lipoprotein concentrations compared to exercising either 24 h before or shortly prior to a meal, suggestive of an important role of lipoprotein lipase (LPL) in the lipid-lowering effect of exercise [35, 36, 54]. Katsanos and Moffatt [32], on the other hand, found a greater effect of exercise versus nonexercise but no significant difference between shortly pre- and postmeal walking. However, the heart rate response to postprandial exercise was higher, suggesting that fasting exercise, even if not more effective, might be more advisable than postmeal exercise.

Fasted exercise seems to rule in favor of postprandial lipemic control even when mixed meals rather than high-fat meals are consumed. According to Enevoldsen et al. [29], 60 min of cycling at 55% VO_2max performed 30 min before a standard mixed breakfast resulted in lower con-

Table 2. Studies comparing premeal and postmeal exercise

Study	Subjects	Exercise bouts vs. meals	Design	Exercise	Meal	Results and conclusions
Colberg et al. [28]	12 T2D subjects	1:1	3 trials: 1 rest day and 2 exercise days; exercise: immediately before or 20 min after dinner	20 min self-paced treadmill walking	Standardized dinner with a moderate glycemic effect	Pre- vs. postmeal exercise: less effective in ↓ the glycemic impact of the evening meal
Enevoldsen et al. [29]	7 young healthy male subjects	1:1	Fasted exercise: 60 min of moderate exercise in the fasted state, standard meal 30 min after exercise, and 150 min of rest; postmeal exercise: standard meal, 60 min rest, 60 min moderate exercise, and 180 min rest	60 min cycling, 55% of VO ₂ max	3.5 ± 0.2 MJ: 60% carbohydrate, 20% fat, and 20% protein	Fasted vs. postmeal exercise: a more favorable lipid metabolism during and after exercise (↑ lipid oxidation, ↓ average integrated increase in arterial TG)
Gaudet-Savard et al. [30]	43 men with T2D	NA	1,555 exercise sessions performed in the fasted state and 0–1, 1–2, 2–3, 3–4, 4–5, and 5–8 h postprandially; capillary BGL before and after the exercise session	60 min at 60% VO ₂ peak	ad libitum	BGL during aerobic exercise was largely dependent on pre-exercise BGL; fasted-state vs. postprandial exercise: a smaller decrease in glycemia, for every premeal BGL group (<6, 6–8, and >8 mmol/l), and a greater ↓ 2–5 h after the last meal
Hashimoto et al. [31]	17 healthy young sedentary women	2:1	2 experimental groups: Exp. 1 (n = 8) – exercise 20 min after test meal, and Exp. 2 (n = 8) – exercise 50 min before meal; a CON day for each group	30 min walking at 50% VO ₂ max	Oral fat tolerance test (OFTT) cream (1 g fat/kg body weight)	Exercise vs. CON: decreased postprandial TG, iAUC-TG, but statistically nonsignificant; chylomicron particles ↓ in the postprandial exercise group
Katsanos and Moffatt [32]	10 untrained healthy young men	1:1	3 trials: CON (high-fat meal), EM (exercise 30 min prior to meal), and ME (exercise 90 min postmeal)	90 min walking, 50% VO ₂ max	4,604 kJ, 95 g fat (81%), 50 g carbohydrate (17%), and 10 g proteins (2%)	Pre- vs. postmeal exercise: same ↓ in postprandial hypertriglyceridemia; lower HR response to exercise
Poirier et al. [33]	19 men with T2D	NA	3 months of training; patients had to record the time interval from the last meal; whole blood glucose was measured before and after every session	60 min at 60% VO ₂ max	Subjects kept their usual dietary habits during the training period	Fasted-state exercise: no clinical impact on blood glucose; postprandial exercise: ↓ in blood glucose, especially if 3–5 h after the last meal
Van Proeyen et al. [34]	27 healthy males	training program + diet	3 parallel groups: CON (on a high-fat diet), fasted (high-fat diet and exercise in the fasted state), and CHO (high-fat diet and exercise with the consumption of carbohydrates before and during exercise)	4 weekly sessions: 2 × 60 min and 2 × 90 min sessions; cycling at an HR corresponding to 70–75% of VO ₂ max + running at 85% HRmax	High-fat diet: increase of about 30% in caloric intake (50% fat, 40% carbohydrate, 10% protein); carbohydrate meal (breakfast): 675 kcal, 70% carbohydrate	Fasted training vs. fed training: is more potent in facilitating adaptations in muscle (GLUT-4, AMPKα phosphorylation, fatty acid enzymes) and to improve whole-body glucose tolerance and insulin sensitivity
Zhang et al. [35]	21 recreationally active young men	1:3	4 trials: CON (high-fat meal only), post- (exercise 1 h after a high-fat meal), 1 h premeal, and 12 h premeal (exercise 12 h prior to high-fat meal)	60 min treadmill walking, 60% VO ₂ max	At 0 h: standard high-fat meal: 980 kcal, 100 g fat; at 8 h: standard meal with 75% carbohydrate; at 12.5 h before the blood sample at 24 h: standard snack: 297 kcal; total: 2,167 kcal, 137.9 g fat (57%), 190.5 g carbohydrate (37%), and 31.5 g protein (6%)	Pre- vs. postmeal exercise: better for postprandial triglyceridemia (↓) and HDL cholesterol (↑); exercise 12 h prior to vs. 1 h prior to a meal: better for postprandial triglyceridemia (↓) and HDL cholesterol (↑)

CON = Control; ↓ = significant decrease; ↑ = significant increase; BGL = blood glucose levels; EM = exercise followed by a meal; ME = meal followed by exercise; HR = heart rate; HRmax = maximal heart rate; NA = nonapplicable.

Table 3. Studies investigating the effect of aerobic exercise on postprandial events

Study	Subjects	Exercise bouts vs. meals	Design	Exercise	Meal	Results and conclusions
Aldred et al. [36]	12 healthy women	1:1	2 trials: CON day – high-fat meal; exercise day – walking session, 15 h before a high-fat meal	120 min walking at $30.9 \pm 1.6\%$ VO_2max	Cereal, fruit, nuts, chocolate, and cream (1.2 g fat/kg)	Exercise vs. CON: ↓ fasting TG, peak TG, and total lipemic response (AUC-TG)
Charlot et al. [37]	9 healthy moderately active men	1:2	2 trials: RT (rest trial) and EX (exercise); 2 meals: standard breakfast and lunch	15 min of progressively increasing intensity exercise + 60 min at 70% VO_2max	2 meals: standard breakfast (1,700–2,900 kJ), and lunch (freely asked)	EX vs. RT: ↓ glycemia during and 25 min after the exercise session; later and higher peak in postlunch glycemia in the EX trial
Farah et al. [38]	10 young sedentary overweight/obese men	1–3:1	3 trials: CON (no exercise on days 1–3 prior to the meal day), EX-1 (fasted exercise session on day 3), and EX-3 (fasted exercise session on days 1–3)	Walking at 50% VO_2max to induce a net expenditure of 33.5 kJ/kg body mass	ad libitum buffet-style breakfast	Exercise vs. CON: attenuated lipemic response to ad libitum meals (relevance in ‘real-world’ settings); exercising on repeated days does not augment this response
Gill et al. [39]	11 healthy women	1:1	3 trials: CON day (high-fat meal), 1-hour walk, and 2-hour walk (the afternoon before the test meal)	60/120 min walk, 50% VO_2max	High-fat meal – 73 kJ/kg, 1.3 g fat, 1.2 g carbohydrate, 0.2 g protein	Beneficial effects of exercise on postprandial metabolism are dose-dependent (related to the duration and energy expenditure of the exercise session)
Gill et al. [40]	19 healthy women	1:1	2 parallel groups: fasting (F) and postprandial (PP); F: exercise day (walking session, 18 h prior to blood samples) and CON day (no exercise); PP: 2 fat tolerance tests the day following exercise (exercise day) or rest (CON day)	120 min walking at 50% VO_2max	73 kJ/kg fat-free mass, 1.3 g fat, 1.2 g carbohydrate, 0.2 g protein	Exercise vs. CON: ↓ fasting and postprandial TG (correlated to exercise-induced LPL activity)
Hardman and Aldred [41]	12 young men and women	1:1	2 trials: exercise day (postprandial walking) and CON day (no exercise)	90 min walking at 40% VO_2max	71 kJ/kg body mass, 1.2 g fat	Exercise vs. CON: ↓ AUC-TG
Herd et al. [42]	8 physically active young men	1:1	2 trials: exercise day (cycling 16 h before test meal) and CON day (no exercise)	90 min of cycling at $62.3\% \pm 1.7\%$ VO_2max	73 kJ/kg body mass, 1.4 g fat, 1.2 g carbohydrate, 0.2 g protein	Exercise vs. CON: ↓ 6-hour AUC-TG; the difference in lipemia was inversely related to the difference in LPL activity
Hostmark et al. [43]	39 healthy women	1:1	2 trials: CON day – high-carbohydrate meal (1 g/kg), no exercise; exercise day – meal + 30 min postmeal exercise; 4 groups according to age and training level	30 min cycling at 70% HRmax	Cornflakes (1 g carbohydrate/kg body weight)	Exercise vs. CON: acutely ↓ BGL to a magnitude similar to hypoglycemic drugs; middle-aged women benefited more from exercise compared to their young counterpart
Kolifa et al. [44]	9 healthy young male volunteers	1:1	2 trials: CON (meal only) and high-intensity exercise prior to meal	60 min of cycling at 70–75% of HRmax	71 kJ/kg: 35% fat (0.66 g/kg), 50% carbohydrate (2.14 g/kg), and 15% protein (0.62 g/kg)	Exercise vs. CON: ↓ plasma TG and total AUC-TG; iAUCs-TG nonsignificant differences

Table 3 (continued)

Study	Subjects	Exercise bouts vs. meals	Design	Exercise	Meal	Results and conclusions
Larsen et al. [45]	9 sedentary males with T2D	1:2	3 trials: CD (CON day – standard meals, 4 h apart), ED (exercise day – exercise + meal), and DD (diet day – reduced calories)	45 min 53% VO ₂ max, after breakfast	CD and ED: 29 kJ/kg (56% carbohydrate, 30% fat, 14% protein); DD, reduced in calories with the amount equivalent to that spent during exercise; lunch: 59 kJ/kg body weight, 53% carbohydrate, 31% fat, 16% protein	Exercise vs. CON: ↓ glycemia + plasma insulin; no effect during and after the following lunch; caloric restriction: same effect as exercise on postprandial glycemia and insulin secretion
Larsen et al. [46]	8 T2D males	1:2	2 trials: CD – CON day (standard meals, 4 h apart) and ED – exercise day	Postbreakfast: 4 bouts: 3 min, 57% VO ₂ max + 4 min, 98.3% VO ₂ max + 6 min rest for each bout	Breakfast: 29 kJ/kg (56% carbohydrate, 30% fat, 14% protein); lunch: 59 kJ/kg (53% carbohydrate, 31% fat, 16% protein)	Exercise vs. CON: ↓ glucose and insulin; this effect is related to energy expenditure rather than the peak exercise intensity; no effect after lunch
Manders et al. [47]	9 T2D subjects	1:3	3 trials: NE (nonexercise), LI (low-intensity exercise), and HI (high-intensity exercise)	Equicaloric bouts: (LI) – 60 min at 35% Wmax, (HI) – 30 min at 70% Wmax + 30 min rest, and (NE) – 60 min seated	3 meals and 3 snacks – 121 kJ/kg/day, 58% carbohydrate, 30% fat, 11% protein	Low vs. high intensity: ↓ prevalence of hyperglycemia throughout the subsequent 24-hour postexercise period
Murphy et al. [48]	10 adults, 45–55 years old	1–3:3	3 trials: 3 meals + no exercise (CON), 3 meals + 10 min brisk walking before each meal (short walks – 30 min total), and 3 meals + 30 min brisk walking (long walk)	3 bouts of 10 min or 1 bout of 30 min brisk walking 60% VO ₂ max	Breakfast: 2.4 MJ, 30 g fat, 58 g carbohydrate, 28 g protein; lunch: 6.14 MJ, 76 g fat, 144 g carbohydrate, 70 g protein; dinner: 3.68 MJ, 46 g fat, 86 g carbohydrate, 41 g protein	Short vs. long walks: no significant differences; both reduce postprandial triglyceridemia and increase fat oxidation
Nygaard et al. [49]	14 healthy women over 50 years of age	1:1	3 trials: CON (rest + carbohydrate meal), Walk 15 (15 min of slow postmeal walking), and Walk 40 (40 min of slow postmeal walking)	Indoor walking, postmeal, level 9 on Borg's RPE scale	Carbohydrate meal: 1 g carbohydrate/kg body weight (cornflakes and milk)	Exercise vs. CON: ↓ 2-hour iAUCs of glucose, ↑ time to peak glycemia; duration of exercise determines the peak glucose response to a meal
Pfeiffer et al. [50]	16 healthy sedentary men	1:2	4 trials: CON day (no exercise), 30 min exercise, 60 min exercise, and 90 min exercise (immediately before the first meal)	30, 60, or 90 min walking, 50% VO ₂ max	2 mixed meals, moderate fat content (0.5 g/kg body weight)	Exercise vs. CON: no effect on postprandial lipemia; duration of exercise: no effect
Pfeiffer et al. [51]	12 healthy untrained young men	1:2	4 trials: CON (no exercise), exercise 420 kJ, exercise 630 kJ, and exercise 840 kJ (immediately before meals)	30 min cycling at a target of 420, 630, or 840 kJ	2 mixed meals, moderate fat content	Exercise vs. CON: no effect on postprandial lipemia; no effect of energy expenditure
Szewieczek et al. [52]	14 T2D subjects vs. 14 healthy CON	1:1	Graded exercise testing 2 h after standard breakfast	Progressive ↑ workload to 85% HR max	Standard breakfast: 30% of the daily caloric demand	T2D vs. CON: ↑ peri-exercise glycemia and ↓ glycemia in the recovery phase; pre-exercise glycemia is the primary predictor of the changes in glycemia during and after effort
Tobin et al. [53]	8 T2D subjects vs. healthy CON	1:1	CON day (high-fat meal + rest) vs. exercise day (high-fat meal + exercise)	60 min of exercise, 90 min after breakfast	680 kcal/m ² ; 84% fat, 8% carbohydrate, 8% protein	T2D vs. CON: exercise ↓ iAUC of triglycerides and insulin

CON = Control; HRmax = maximal heart rate; Wmax = maximal power.

centrations and an average integrated increase of plasmatic very low-density lipoprotein triacylglycerol (VLDL-TG), a lower triacylglycerol area under the curve (TG-AUC), and lower concentrations of plasmatic insulin compared to the same exercise 60 min postprandially. Also, prebreakfast cycling produced higher whole-body and adipose tissue lipolytic rates [29]. Recently, Hashimoto et al. [31] indicated that moderate-intensity exercise 20 min after a moderate-fat meal might be more favorable in terms of exogenous TG. It should be mentioned, however, that the authors clearly stated that due to the small number of participants and the specific design of the study the results should be interpreted with caution.

It may be concluded, from the studies comparing the two modalities, that exercising in the fasted state rather than in the fed state more effectively attenuates the lipemic effect of a meal, especially when high in fat content. Accordingly, the majority of studies investigating the effect of exercise on the TG response to a meal focus on different amounts of exercise performed in the afternoon prior to a test meal. The beneficial effect of prior exercise on postprandial lipemia could probably be related to the activation of either muscular or plasmatic LPL. In fact, changes in muscle LPL activity and plasmatic LPL concentration appear to be well correlated to changes in triglyceridemia, which makes this enzyme a plausible, yet partial, explanation for the TG-lowering effect of exercise. [40, 42]. Considering that exercise-induced LPL activation does not occur until 4 h postexercise and lasts for 18–24 h after an exercise session [55–57], LPL can certainly not be responsible for changes in TG levels outside this time frame. The latter may explain, in part, the finding that exercise results in a better lipidic response when performed 12 h prior, rather than 1 or 24 h prior, to a high-fat meal in healthy [35] or hypertriglyceridemic individuals [54].

There is contrasting evidence regarding the lipid-lowering effect of fed-state exercise. Zhang et al. [35] and Tobin et al. [53] found no effect of postmeal moderate-intensity aerobic exercise after a high-fat meal in healthy individuals. Conversely, two other studies found a beneficial effect of postmeal exercise on the lipemic response to a high-fat meal [32, 41]. However, as previously pointed out in the study of Katsanos and Moffatt [32], prior exercise could be more advisable due to the fact that it provokes less discomfort and cardiac response [32]. Therefore, postmeal exercise might also have an attenuating effect on postprandial lipemia, probably less pronounced and certainly involving different physiological mechanisms compared to exercise in the fasted state.

With regard to postprandial lipemic control, several investigations have compared fasted and postmeal exercise effects in healthy adults. The situation is completely different as far as diabetic patients are concerned, which makes our analysis rather difficult in the case of such patients. There is no study we know of that investigates the difference in lipemic response to a meal when exercise is performed prior to or after the meal in diabetic patients. It would be reasonable to assume that, as diabetes is a metabolic disorder involving primarily the metabolism of energetic substrates like glucose and lipids, the lipemic response to both meals and exercise might differ in diabetic patients.

Accordingly, diabetic patients, compared to a healthy control group, show higher basal levels of plasmatic TG and glucose, and these levels increase twice as much after a high-fat meal [53]. Alssema et al. [58] reported that a high-carbohydrate meal elicits greater TG, glucose, and insulin responses in T2D postmenopausal women when compared to age-matched healthy counterparts. One hour of moderate-intensity exercise, introduced after a fatty meal, is reported to attenuate meal-induced hyperlipidemia, reducing the total TG and VLDL-TG, in diabetics but not in healthy individuals [53]. Thus, the findings in normal individuals cannot be always transferred to those affected by disease.

Other Factors Influencing the Hypolipemic Effect of Exercise

In the setting of high-fat meals, the results have constantly been in favor of exercise and, as previously mentioned, if exercise sessions were to take place with sufficient time prior to a meal, their lipid-lowering effects would be more evident [32, 35, 36, 39, 40, 42, 54, 59, 60], with no significant difference between continuous and accumulated bouts [48]. Such results cannot be completely transferred to the generally recommended mixed, moderate-fat meals an adult is to consume in order to preserve health [61].

Meal composition and exercise amount are important additional factors influencing the effect of exercise. Contrasting results have been reported from studies investigating the effect of moderate-intensity exercise or its caloric equivalent on the lipemic response to a moderate-fat meal. Pfeiffer et al. [50, 51] investigated the effect of ‘moderate-dose’ exercise performed before a moderate-fat meal and the yielded results suggested that exercise might lose its lipemic lowering effect in such conditions. Also, postprandial lipemia remained unaltered when increasing the ‘dose’ of exercise, i.e. duration [50] or energy ex-

penditure [51]. Kolifa et al. [44], on the other hand, found a lowering effect of prior exercise on total TG but not the TG response to a meal when a moderate-fat-containing meal is consumed 14 h after a cycling session. The same appears to be true when an ad libitum breakfast and lunch are consumed the day after an exercise session of relatively high energy expenditure (33.5 kJ/kg body mass) [38]. This free feeding pattern is certainly closer to real life than standard laboratory meals, and the fact that exercise conserved its lipid-lowering effect independently of meal characteristics suggests that when such high doses of exercise are administered to healthy adults, meal size and composition become of secondary importance. In fact, Gill et al. [39] found out that exercise showed a dose-dependent, exercise-specific effect on TG, which further supports the finding of Farah et al. [38]. Nevertheless, the duration of exercise necessary to accumulate 33.5 kJ/kg body mass in the latter was between 65 and 110 min, which makes it rather unlikely to be performed on a daily basis in order to attenuate postmeal hyperlipidemia.

In summary, it can be said that the effect of prior exercise on lipidemia in healthy adults cannot be determined by a single factor but is rather determined by the mutual interplay of exercise dose and meal size and composition. The response to a big, high-fat meal is likely to be influenced even by moderate doses of exercise, whereas the response to a moderate-fat meal is not. Likewise, when high amounts of energy expenditure are achievable, meal characteristics may be less important. The latter could be of comfort on touristic trips when, along with sightseeing that involves long walks, one can also enjoy the traditional cuisine without guilt.

Glycemic Response to Aerobic Exercise in Healthy Individuals – Fasted versus Fed

Postprandial glycemia, or more precisely hyperglycemia, remains a central issue in the management of diabetes. Glycemia is easily modulated by lifestyle and pharmacological interventions, with the former as important as drugs in diabetic patients [43] and the single most relevant intervention in healthy individuals.

Naturally, research on glycemic control done on diabetic patients outweighs that done on healthy nondiabetic subjects. Results from a few studies on healthy individuals will shortly be examined as a basis of comparison between the two conditions. Very few studies compared the glycemic responses to exercise performed pre- or postmeals in healthy individuals. A specific study that compares these two exercise timings is the study from

Van Proeyen et al. [34]. It being a longitudinal study, its results show the cumulative effect of regular training, either in the fasted state or in the fed state, when on a hypercaloric, high-fat diet. This kind of diet may not be the typical eating pattern of healthy individuals whose purpose is to preserve their health. Nevertheless, for those who in the long or short term consume high volumes of fat-rich food, exercise timing might make the difference. Indeed, the study in question manages to demonstrate that 4 days per week of endurance exercise training performed in the fasted state is significantly superior to fed-state exercise in terms of whole-body glucose tolerance, insulin sensitivity, and muscle adaptations, i.e. AMP-activated protein kinase α phosphorylation, GLUT-4 (glucose transporter 4), etc. [34].

Evaluating the immediate responses to a similar amount of endurance exercise performed before carbohydrate intake, it appears that such exercise results in no significant main effect on plasma glucose and insulin, although it might alter the kinetics of these parameters [62].

Postprandially performed exercise, on the other hand, might not offer the same results. In healthy women, light to moderate-intensity walking or cycling immediately after a high-glycemic breakfast (i.e. cornflakes and milk, 1 g carbohydrate per kg body weight), attenuates the glycemic response (incremental area under the curve; iAUC) to a meal [43, 49] compared to rest. When comparing 15-min bouts with 40-min bouts, the hypoglycemic effect appears to be proportional to the duration in the same way it is proportional to the intensity, leading to the suggestion that this lowering effect is primarily determined by energy expenditure during exercise [49]. Furthermore, those who might be benefiting more from 30–40 min of moderate-intensity exercise, or shorter-duration but higher-intensity exercise, are individuals showing more elevated glycemic responses at rest [49, 52] and sedentary, middle-aged subjects, the latter compared to trained, young subjects [43]. Even more interesting is the fact that the glucose-lowering effect of postmeal exercise is reported to be comparable to that of hypoglycemic drugs [43]. A more vigorous postprandial exercise has been reported to transiently increase blood glucose values compared to pre-exercise [52]. In contrast, Charlot et al. [37] reported that 75 min of high-intensity cycling, compared to rest, yield sustained lower glycemia throughout the exercise session and may also exert an influence on the following meal, delaying peak postlunch glycemia with no significant difference in total glucose AUCs. However, the generalizability and practical relevance of such results may

need further investigation. What we can almost certainly affirm is that, in the immediate term, moderate volumes of exercise produce better glycemic effects in healthy adults if performed after a meal, compared to preprandial exercise.

Effect of Exercise on Postprandial Glycemia in Diabetic Individuals: Time Interval from a Meal

As we previously emphasized, diabetic patients differ from healthy subjects in their metabolic and hormonal responses to meals. Accordingly, T2D patients respond more abruptly to either a high-carbohydrate meal or a high-fat meal, in terms of glucose and insulin iAUCs, when compared to nondiabetic subjects [53, 58].

Applying exercise as a treatment in diabetic patients involves two major issues. Firstly, exercise should be safe. Secondly, it should be effective. Fulfilling these two criteria would potentially prevent any risks of acute (hypoglycemia) or chronic (mainly cardiovascular) complications and thus successfully manage diabetes. It would be rather intuitive to think that, as both exercise and meals provoke a glycemic response, the time interval from a meal would be tightly connected to the safety and effectiveness of exercise. In addition, one particular aspect that should always be taken into consideration when examining blood glucose control in diabetic patients is the categorization of effects according to the oral hypoglycemic drugs being taken by patients in the meantime.

As for the safety of exercise in T2D patients, the major concern refers to exercising in the fasted state, especially in patients using insulin-secreting drugs, due to the risk of eliciting hypoglycemia, with the latter being a recognized precipitating factor for myocardial ischemia [63]. However, there is convincing evidence that the actual risk of fasted exercise causing hypoglycemia is virtually inexistent for diabetes patients on diet only and/or oral hypoglycemic drugs, sulfonylureas included [33, 64–68]. Even more interesting are the findings of Gaudet-Savard et al. [30] showing that the glycemic response to exercise is primarily determined by pre-exercise plasmatic concentrations of glucose. Hence, the same fasted exercise may either decrease or have no effect on glycemia, depending on the pre-exercise starting point.

With regard to the effectiveness of exercise in lowering blood glucose, it has been repeatedly demonstrated that 60 min of cycling at 60% $\text{VO}_{2\text{max}}$ is most effective in lowering blood glucose when performed postprandially [30, 33, 68]. These results apply to both standard (mixed meal) and nonstandard (ad libitum) meal conditions [33, 68]. The hypoglycemic effect of exercise appears to be greatest

in the late postprandial period, i.e. 4–5 h, especially in patients on a combination of metformin and sulfonylureas, or sulfonylureas alone [30, 33]. As with the effect of exercise in the fasted state, in the fed state also, postexercise glycemia will depend on the pre-exercise blood glucose levels [30].

Further dividing the postprandial period into pre- and postmeal times, evidence from Colberg et al. [28] demonstrates that as little as 20 min of postmeal, but not premeal, self-paced walking significantly attenuates the glycemia after a standard dinner.

The beneficial effects of aerobic exercise are generally attributed to its intensity [69]. However, evidence from Larsen et al. [45, 46] and Manders et al. [47] shows that higher intensities are not necessarily a synonym of better postprandial glycemic control. On the contrary, apart from being a more comfortable and feasible option for diabetic patients, moderate to low intensity iso-energetic exercise is not different in terms of glycemic response, compared to higher intensities. Indeed, high and low intensities, when matched for energy cost, produce similar effects on postprandial and nocturnal glucose concentrations [47]. Furthermore, low-intensity, but not high-intensity, exercise lowers the 24-hour glucose responses and prevalence of hyperglycemia, as demonstrated by continuous monitoring of blood glucose [47].

Discussion and Conclusions

Statements like: ‘exercise is good for your health’ or ‘exercise may prevent chronic disease’, have become common knowledge nowadays, but while life is becoming faster – fast food, fast transportation, fast clicks – moving is becoming slow. While man works to perfect technology, lifestyle takes a few steps back and chronic disease thrives. It is in this era that time seems to be the main unresolved issue with regard to inactivity. Fortunately, time is not only a problem – it may also be a solution.

In the studies presently reviewed, timing appeared to interfere with the resulting metabolic effect of an exercise session. The same amount of aerobic exercise (generally referring to the total energy expended during exertion) was demonstrated to produce completely different results, ranging from no effect to significantly lower triglyceridemia or glycemia.

Interestingly, in healthy individuals, exercising in the fasted state rules strongly in favor of TG control [32, 35, 36, 39, 40, 42, 54, 59, 60], leaving glycemia basically unaltered [33, 64–68]. On the other hand, regularly training

in this state prevents weight gain and lipid-induced insulin resistance in people consuming hypercaloric and high-fat diets [34].

These results might be of particular relevance in those countries where the traditional diet is very rich in fat. Hence, regular exercise before breakfast might be the most effective in overcoming the lipid-induced detrimental effects of such a diet. When high-fat content is only occasional among the usual meals of healthy individuals, exercising in the morning or in the evening before an occasional high-fat meal would probably bring more 'cheers' to that family Sunday lunch. Of note, however, is the observation made by Pfeiffer et al. [50, 51] that the same type and amount of exercise is least likely to have significant effects on postprandial TG when the lipemic impact of meals is only moderate to low. Hence, it can be affirmed that in specific life settings, such as high-fat meals, fasted-state exercise could probably be more effective in attenuating the diabetogenic and atherogenic effect of postprandial phenomena, and consequently in preventing chronic disease.

The main concern in the case of iso- or hyper-caloric mixed meals, generally with moderate fat content but high in carbohydrate (50–60%), would be postprandial hyperglycemia rather than postprandial lipemia. Concordant results in healthy and diabetic individuals clearly demonstrate that the glycemic response to mixed meals is most effectively attenuated by postmeal exercise [30, 33, 43, 49, 62, 68]. As little as a 20-min walk after a meal [28] holds the potential to prevent cardiovascular disease and diabetes progression.

Certainly, the aforementioned effects are dose dependent, and modulations of exercise timing with the intent to optimize metabolic control are to be considered as an adjunct of the most powerful determinant of the metabolic effect – energy expenditure. As formerly demonstrated, the amount of energy expended in an activity majorly determines the benefit in lipemia and glycemia, making exercise intensity tradable with and as important as duration [39, 45–47]. This concept becomes very important as we consider the array from young to old adults and from healthy to diabetic individuals. For healthy young adults who cannot afford to spend much time exercising, it could be more feasible to engage in short, intense bouts of exercise, whereas in old diabetic patients, where high-intensity exercise might not always be indicated or pleasant, trading intensity for duration would be as effective. Moreover, such an approach in these subjects might prove safer and sometimes more effective in terms of specific aspects of glycemic control [47].

In summary, once an optimal exercise 'dose' is achieved by healthy or diabetic individuals, modulating exercise timing might further optimize the metabolic benefit of aerobic exercise. Hence, modulating 'dose-related' parameters of exercise – i.e. intensity and duration – and the timing of a bout, one can flexibly adjust exercise sessions according to real-life limitations and situations. For instance, in the case of working healthy adults for whom lack of time is probably the main reason for skipping exercise sessions, a high-intensity bout of short duration might be a worthy option. Moreover, in a setting of either habitual or occasional high-fat meals that same session would be greatly beneficial if performed in the fasted state. Differently, in diabetic patients for whom postprandial glycemia is the main treatment target, postmeal exercise might aid in reaching the target. It would seem sensible to speculate that dividing a daily session into two parts, one in the fasted state and one in the postprandial state, could provide maximal benefit for both triglyceridemia and glycemia. The latter, if true, would be of particular relevance to hypertriglyceridemic diabetic patients, but this issue remains to be addressed by future research.

We can now provide an answer to the question 'should exercise be done before or after a meal?'. Aerobic exercise should be performed before or after a meal, depending on the meal composition and metabolic outcome. Premeal exercise should be done to control lipemia and postmeal exercise to manage hyperglycemia.

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