Μηχανισμοί της υποτριγλυκεριδαιμίας της άσκησης

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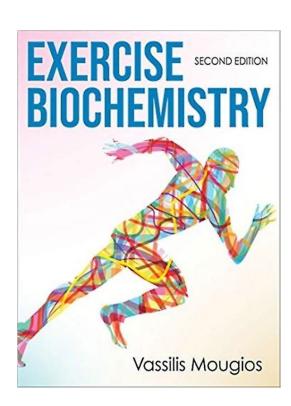




Δήλωση σύγκρουσης συμφερόντων

Κανένα οικονομικό συμφέρον.

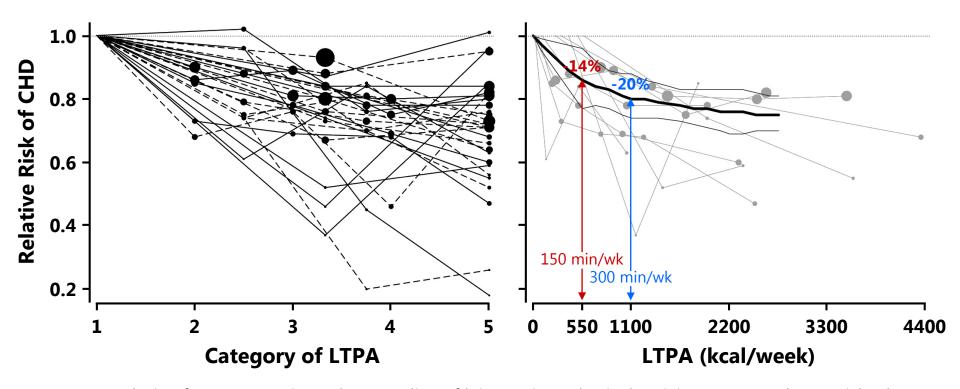
Ωστόσο, ...



Περίγραμμα ομιλίας

- Άσκηση, καρδιαγγειακά και τριγλυκερίδια
- Χαρακτηριστικά της υποτριγλυκεριδαιμίας της άσκησης
- Αλλαγές στο μεταβολισμό των VLDL και μηχανισμοί της υποτριγλυκεριδαιμίας της άσκησης

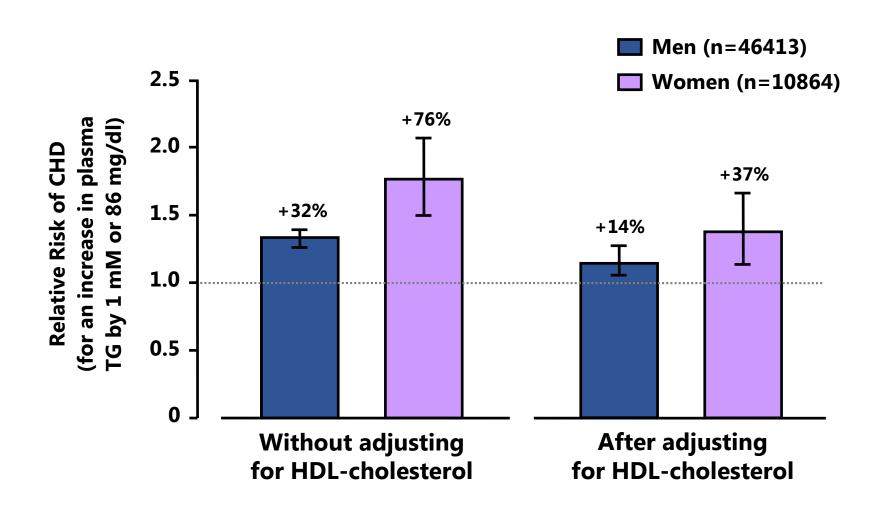
Η τακτική σωματική δραστηριότητα ελαττώνει τον κίνδυνο καρδιαγγειακών με δοσοεξαρτώμενο τρόπο



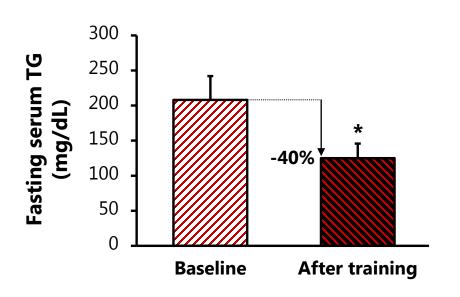
Meta-analysis of 33 prospective cohort studies of leisure-time physical activity (LTPA) and CHD risk. The summary risk indicated a **26% risk reduction** (R=0.74, 95%CI: 0.69–0.78) between the most physically active group and the referent group.

Left: Dose-response relation between LTPA, assessed categorically, and CHD risk (30 comparisons [26 studies] of 56 comparisons [33 studies]). The size of the data point corresponds to the study sample size. Dashed lines indicate studies with LTPA categorized quantitatively; solid lines, studies with LTPA categorized categorically. **Right:** Dose-response relation between quantitative estimates of LTPA, in kilocalories per week, and CHD risk (10 comparisons; 9 studies).

Αυξημένες συγκεντρώσεις τριγλυκεριδίων αυξάνουν τον κίνδυνο καρδιαγγειακών με δοσοεξαρτώμενο τρόπο



Η τακτική σωματική δραστηριότητα ελαττώνει τις συγκεντρώσεις των τριγλυκεριδίων



Washington University School of Medicine in St. Louis

Obituary: John O. Holloszy, former director of applied physiology, 85

Considered the father of modern exercise biochemistry

by Jim Dryden • July 25, 2018

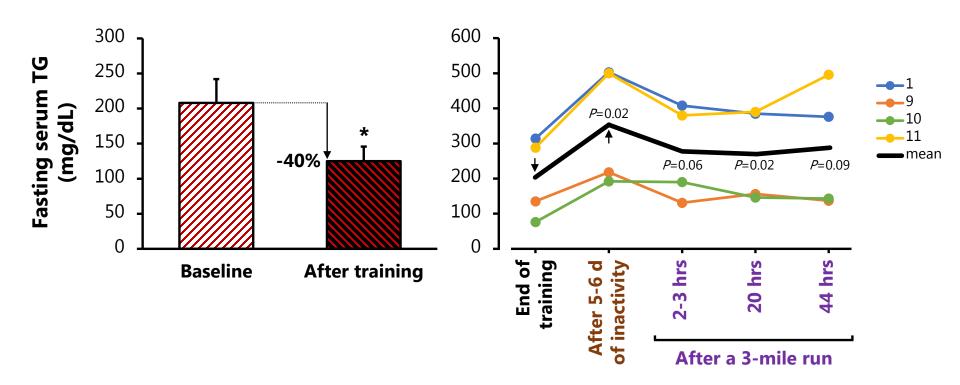


Holloszy

14 sedentary but non-obese men aged 35–55 years were studied before and after a six-month exercise training program (progressively more strenuous endurance calisthenics and distance running—2 to 4 miles—for an average of 3.35 times per week). Body weight remained stable. Four of these men were asked to remain inactive for 5-6 days after the end of the training program and then performed a 3-mile run. Results from these studies demonstrated that the hypotriglyceridemic effect of exercise is **acute** (manifests after a single bout of exercise and is not the result of repeated exercise sessions, i.e. training) and **short-lived** (lasts for 1-2 days).

Είναι λοιπόν πιθανό ότι η καρδιοπροστατευτική δράση της τακτικής σωματικής δραστηριότητας οφείλεται εν μέρει στην ασκησιογενή ελάττωση των τριγλυκεριδίων στο αίμα

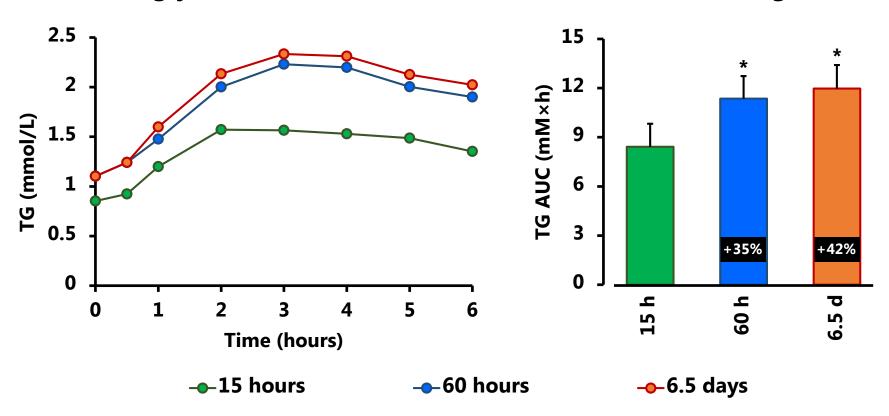
Η υποτριγλυκεριδαιμία της τακτικής άσκησης εμφανίζεται άμεσα και δεν είναι απάντηση στη χρόνια προπόνηση



14 sedentary but non-obese men aged 35–55 years were studied before and after a six-month exercise training program (progressively more strenuous endurance calisthenics and distance running—2 to 4 miles—for an average of 3.35 times per week). Body weight remained stable. Four of these men were asked to remain inactive for 5-6 days after the end of the training program and then performed a 3-mile run. Results from these studies demonstrated that the hypotriglyceridemic effect of exercise is **acute** (manifests after a single bout of exercise and is not the result of repeated exercise sessions, i.e. training) and **short-lived** (lasts for 1-2 days).

Η υποτριγλυκεριδαιμία της τακτικής άσκησης είναι βραχύβια

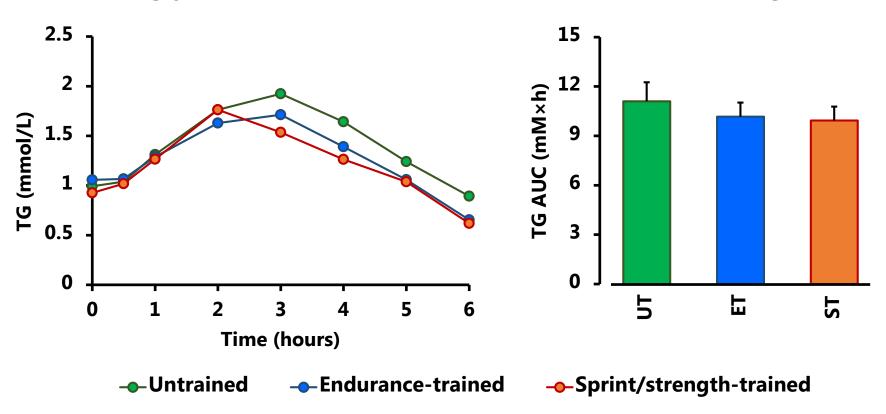
Plasma triglyceride concentrations before and after meal ingestion



10 professional athletes, aged 18–55 years, were studied 15 h, 60 h, and 6.5 days after their last training session; plasma TG concentrations were measured before and after a high-fat meal (69% fat, 27% carbs, 4% protein). Fasting and postprandial plasma TG concentrations increased by approximately 30% and 35-42% after 60 hrs and 6.5 days without exercise, respectively.

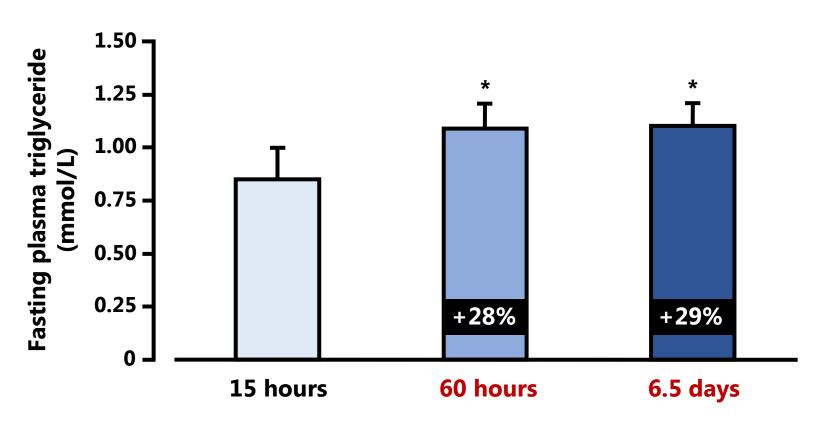
Η υποτριγλυκεριδαιμία της τακτικής άσκησης δεν είναι εμφανής μετά από 2-3 μέρες χωρίς προπόνηση

Plasma triglyceride concentrations before and after meal ingestion



11 untrained men, 11 endurance-trained men (for 6.5 years; currently: 11 times/week), and 10 sprint/strength-trained men (for 9 years; currently 5.5 times/week), aged 18-35 years, with body fat ≤28%, were studied **60 hours after their last training session** (for the athletes); plasma TG concentrations were measured before and after a high-fat meal (69% fat, 27% carbs, 4% protein).

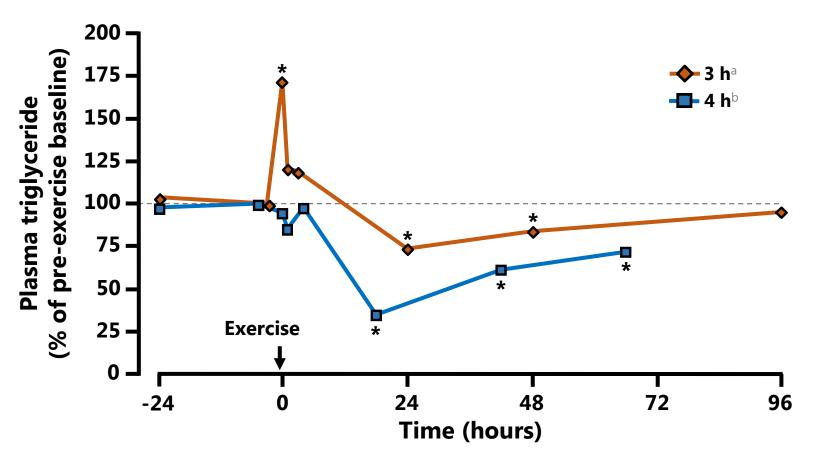
Η υποτριγλυκεριδαιμία της άσκησης στο μεταπορροφητικό στάδιο (νηστεία) είναι βραχύβια



Time after the last exercise training session

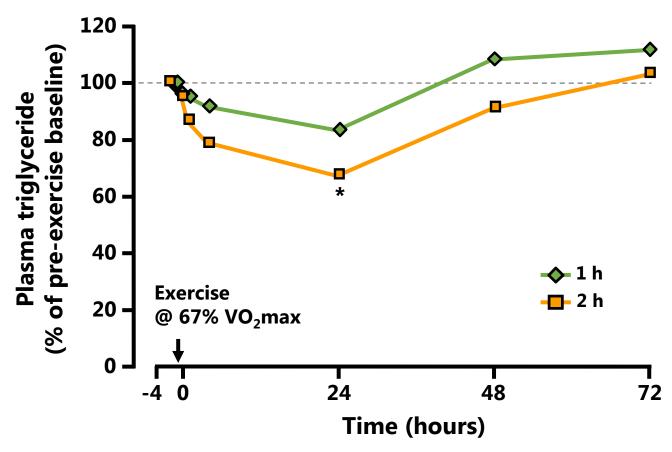
10 professional athletes, aged 18–55 years, were studied 15 h, 60 h, and 6.5 days after their last training session; fasting plasma TG concentrations increased by \sim 30% after 60 hrs and 6.5 days without exercise.

Εμφανίζεται με καθυστέρηση 12-24 ωρών από το τέλος της άσκησης



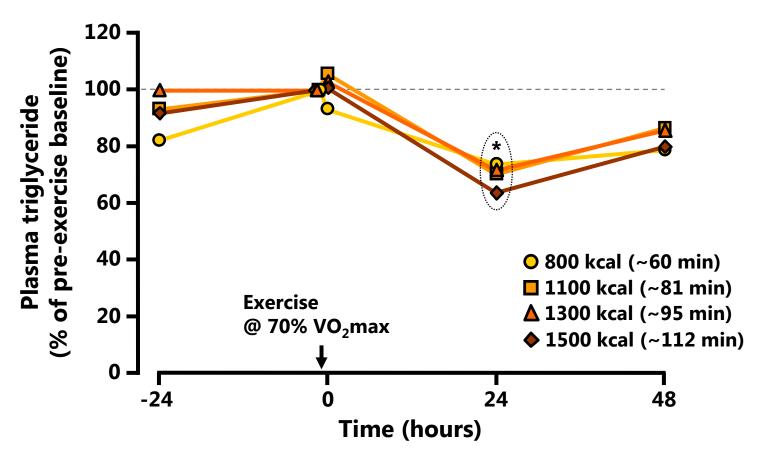
^a14 recreationally active men, aged 20–28 years, ran for 3 h at 75% of lactate threshold; ^b12 trained men, aged 24–50 years, ran 42 km at race pace which took, on average, 3.9 h for completion. The exercise-induced reduction in fasting plasma TG concentration occurs with a delay of 12–18 h and lasts for 2–3 days (time 0 is immediately post-exercise).

Εμφανίζεται πάνω από κάποιο κατώφλι άσκησης



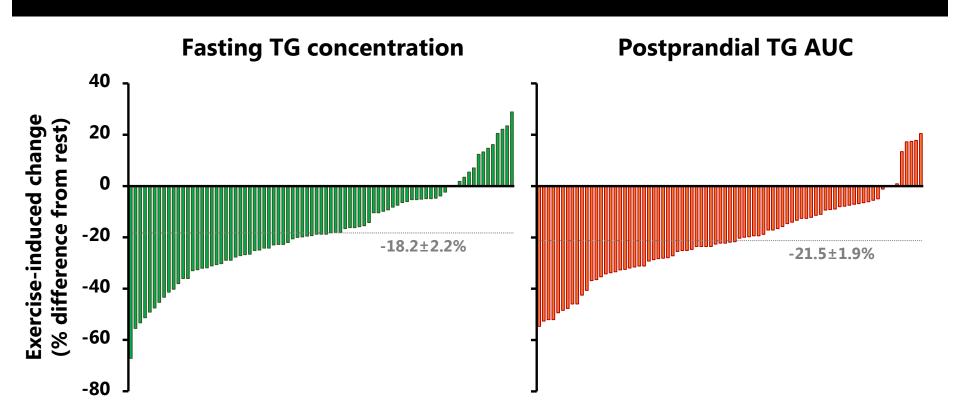
9 trained subjects, aged 18-37 years, cycled for 1 h and 2 h at 67% of VO_2 max (time 0 is immediately post-exercise). A certain threshold of energy needs to be expended during exercise for hypotriglyceridemia to manifest, whereas less exercise does not significantly lower fasting plasma TG concentrations.

Κάνει plateau πάνω από κάποιο άλλο κατώφλι άσκησης



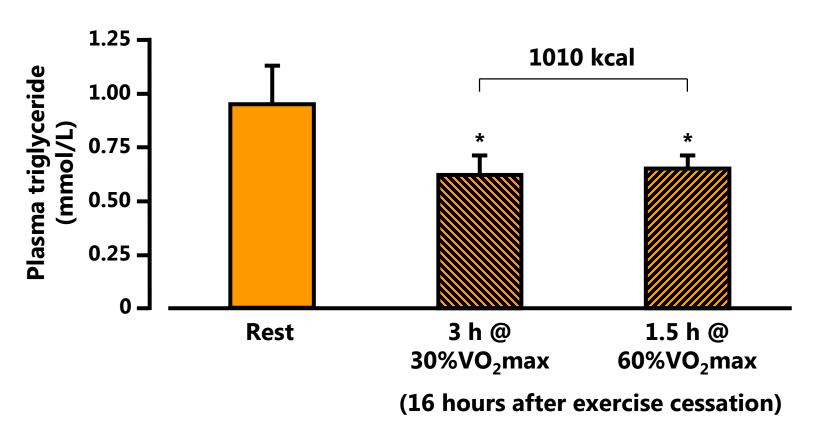
11 trained men, aged 21–44 years, ran at 70% of VO_2 max until 800, 1100, 1300, and 1500 kcal were expended (time 0 is immediately post-exercise). The hypotriglyceridemic effect of exercise plateaus after a certain energy expenditure threshold is achieved; more exercise does not elicit greater reductions in plasma TG concentrations.

Έχει μεγάλη διακύμανση μεταξύ διαφορετικών ατόμων



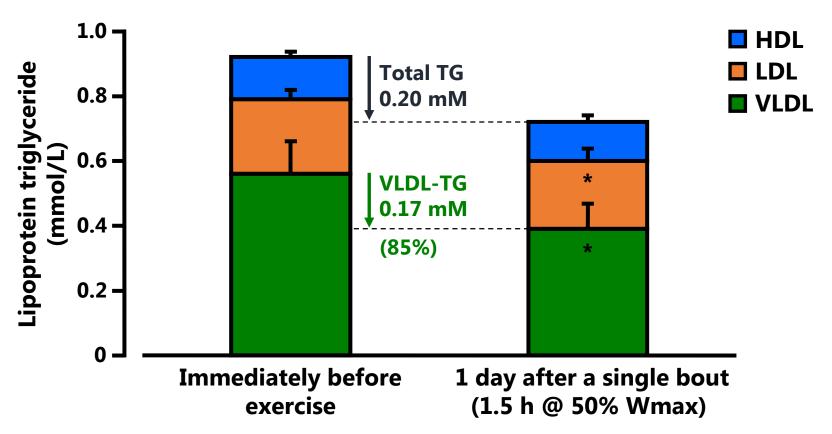
81 subjects (38 men and 43 women; aged 21-64 years, BMI 23.9 \pm 0.3 kg/m², VO₂max 41.2 \pm 1.1 ml/kg·min) participated in two 6-hour oral fat tolerance tests (17 kcal/kg BW; 66% from fat, 29% from carbohydrate, 5% from protein), in random order separated by 5-10 days. On the previous afternoon, they completed a single 90-minute bout of exercise (walking, jogging or running on a motorized treadmill, or cycling on a stationary ergometer) at moderate intensity (61.9 \pm 0.4% of VO₂max), or an equivalent period of rest.

Εξαρτάται από την ενεργειακή δαπάνη της άσκησης (διάρκεια και ένταση)



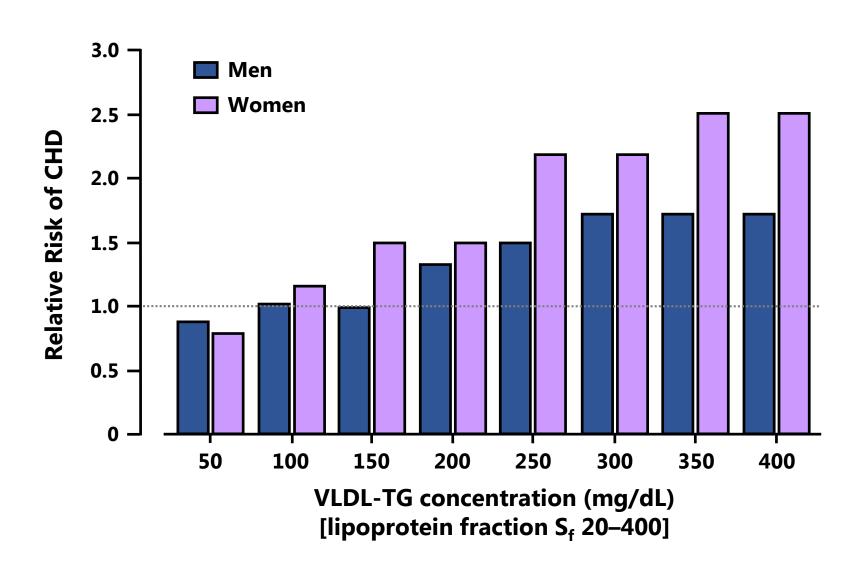
9 recreationally active men and women, aged 25–32 years, exercised for 1.5 hrs at 60% of VO_2 max (1020 kcal) or 3 hrs at 30% of VO_2 max (1000 kcal), or rested, and measurements were performed 16 h later. Exercise intensity and duration are interchangeable when the total energy expenditure is held constant, in that they result in similar reductions in fasting plasma TG concentrations.

Οφείλεται κυρίως σε μειωμένη συγκέντρωση τριγλυκεριδίων στις VLDL



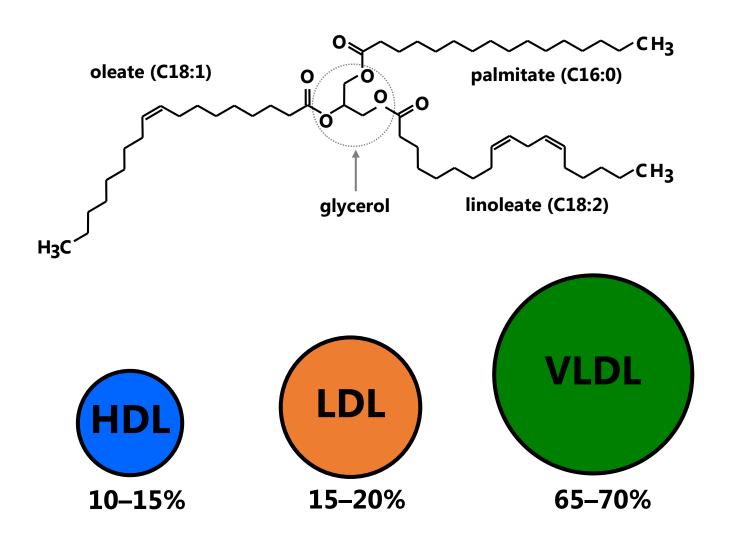
10 recreationally active men, aged 24–33 years, exercised for 1.5 h at 50% of maximal workload and fasting blood samples were collected before and 1 day after exercise for lipoprotein fractionation. The lowering of total plasma TG concentration the day after exercise is primarily due to reduced TG concentrations in VLDL with little if any change in TG concentration in LDL and HDL.

Αυξημένες συγκεντρώσεις VLDL-TG αυξάνουν τον κίνδυνο καρδιαγγειακών

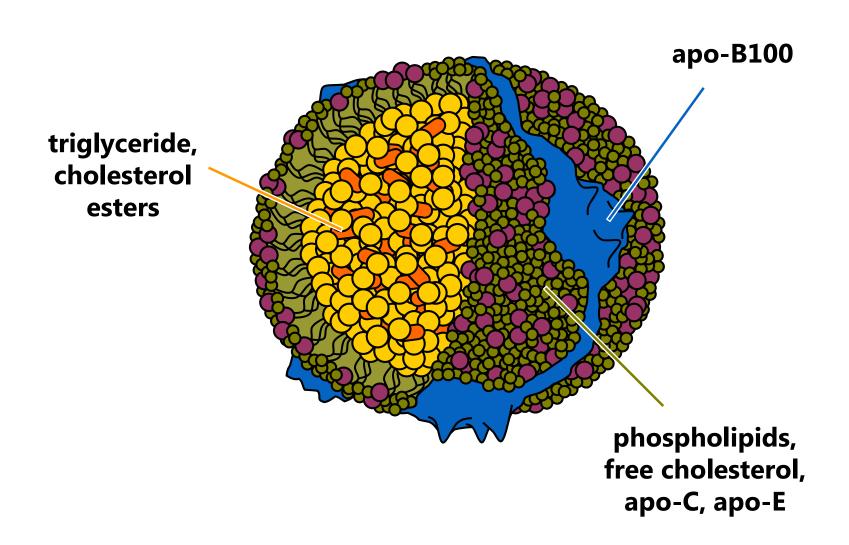


Τι είναι οι VLDL;

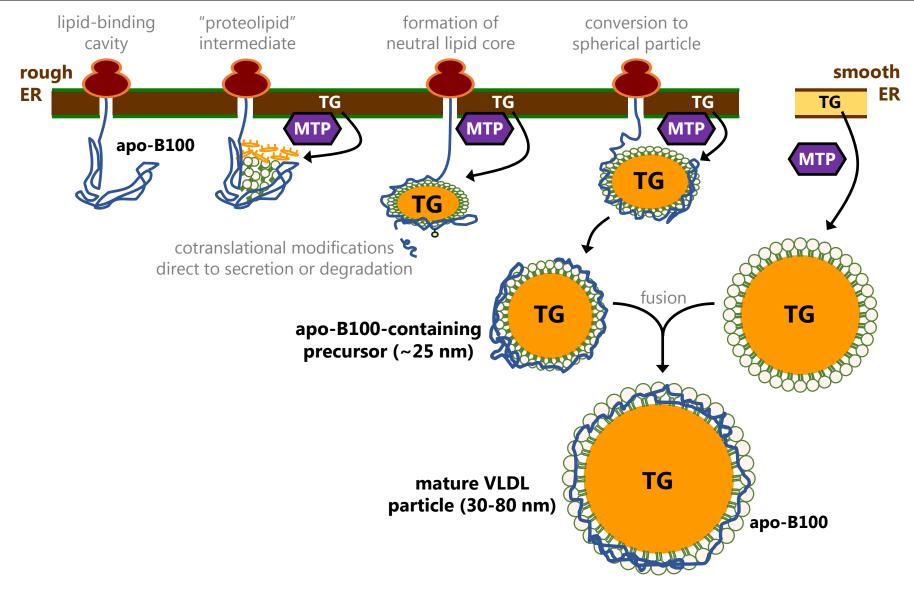
Δομή των τριγλυκεριδίων και μεταφορά τους στο αίμα κατά το στάδιο της νηστείας



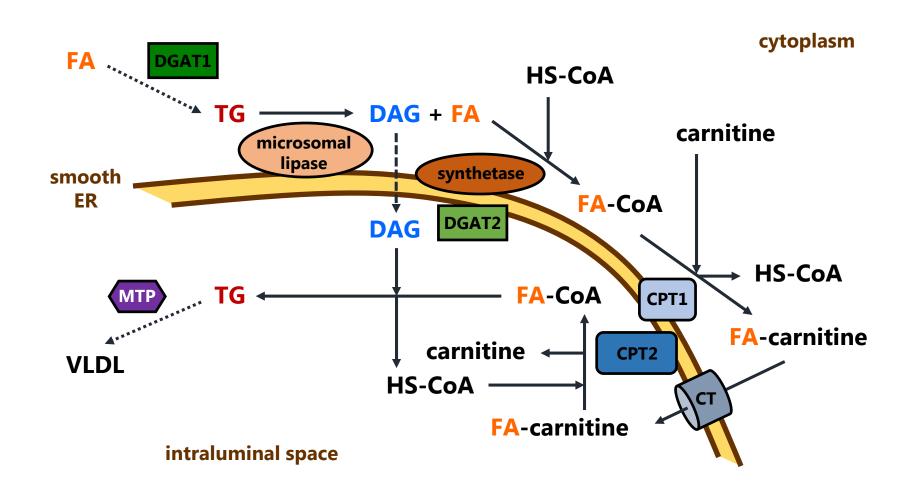
Δομή των λιποπρωτεϊνών πολύ χαμηλής πυκνότητας (VLDL)



Σύνθεση των VLDL στο ενδοπλασματικό δίκτυο σε δύο στάδια



Προέλευση των τριγλυκεριδίων των VLDL: λιπόλυση και επανεστεροποίηση



Ομοιόσταση των VLDL-TG: η απλή εικόνα



When the concentration in the bloodstream is constant (e.g. in the postabsorptive state), the rate of influx must equal the rate of efflux.

Ποιοι είναι οι πιθανοί μηχανισμοί με τους οποίους η άσκηση ελαττώνει τη συγκέντρωση των VLDL-TG;

Increased VLDL-TG removal from plasma

Skeletal muscle LPL mass/activity

Skeletal muscle LFL mass/activity

Clearance of exogenous TG (IVFTT)

Seip & Semenkovich (1998) Exerc Sport Sci Rev 26:191 Kiens & Richter (1998) Am J Physiol 275:E332

> Sady et al (1986) J Am Med Assoc 256:2552 Annuzzi et al (1987) Metabolism 36:438

Reduced VLDL-TG secretion from the liver

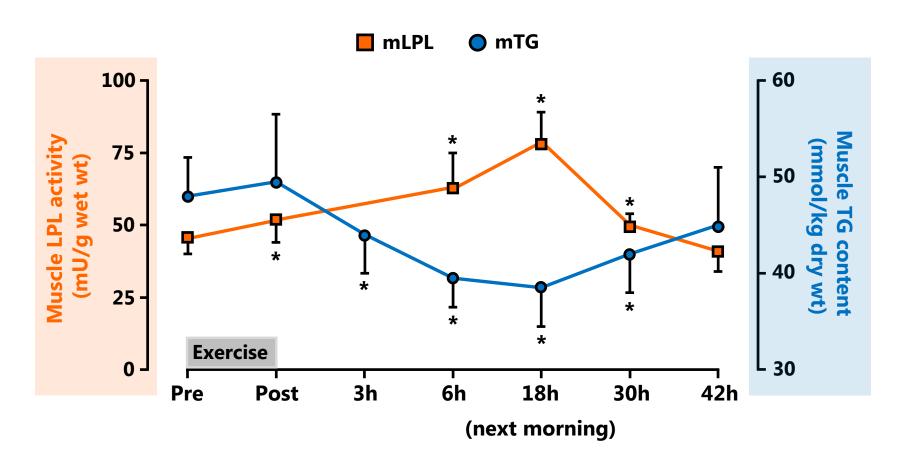
Animal studies; isolated hepatic tissue

Simonelli & Eaton (1978) Am J Physiol 234:E221 Mondon et al (1984) J Appl Physiol 57:1466

Reduced [TG] without changes in mLPL or IVFTT k

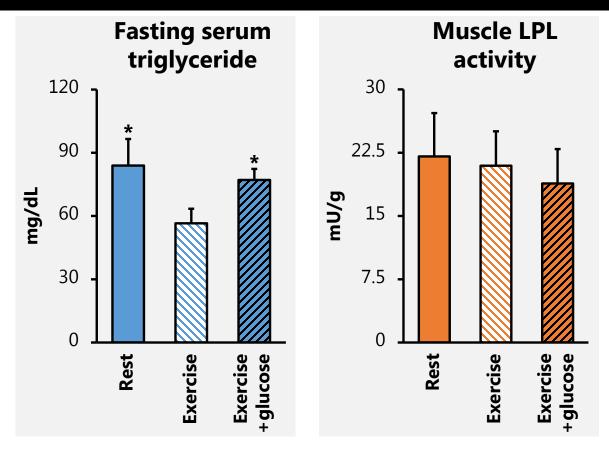
Herd et al (2001) Metabolism 50:756 Gill et al (2001) Eur J Clin Invest 31:201

Μία συνεδρία εξαντλητικής άσκησης αυξάνει τη δραστικότητα της λιποπρωτεϊνικής λιπάσης στο μυ



8 male athletes completed glycogen-depleting exercise (20 min at 75% of VO_2 max followed by ~90 min of 2-min stages at 50%-90% of VO_2 max); no other exercise for 2 days before and after, and controlled diet; biopsies from the vastus lateralis muscle for LPL and TG analyses.

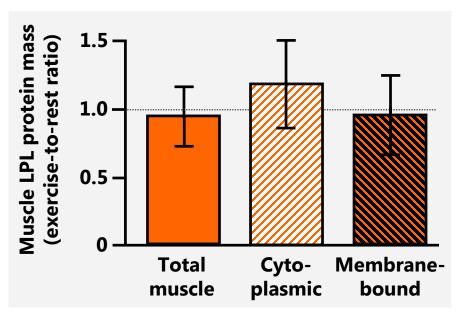
Η υποτριγλυκεριδαιμία της άσκησης μπορεί να εμφανιστεί απουσία αυξημένης LPL στο μυ

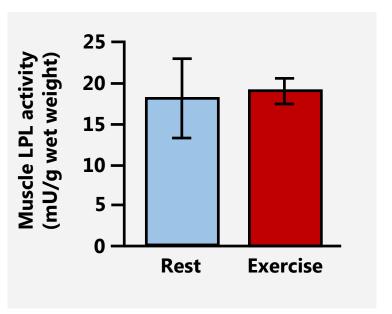


8 moderately active men (age 26.9 ± 1.4 years, VO₂peak 46.8 ± 1.7 mL/kg·min, BMI 26.0 ± 1.3 kg/m², body fat $15.2\pm1.8\%$) performed three trials in random order separated by seven days: evening rest (control), evening exercise without subsequent food intake (cycling for 90 min at 70% VO₂peak, followed by ten 1-min full effort sprints interspersed with 1 min of resting recovery; total EE ~1500 kcal), and evening exercise with subsequent glucose intake (~370 g) to replace all expended energy. The next morning a muscle biopsy and a fasting blood sample were obtained.

Η υποτριγλυκεριδαιμία της άσκησης μπορεί να εμφανιστεί απουσία αυξημένης LPL στο μυ

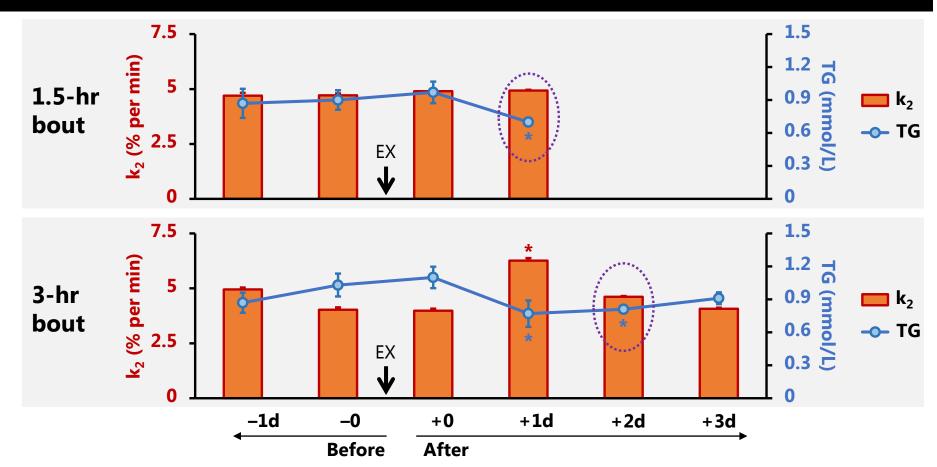
Lower (by 20-30%) fasting and postprandial triglyceride concentrations 12-24 hours after a single bout of prolonged (90-120 min) but non-exhaustive aerobic exercise at moderate intensity are not accompanied by changes in protein mass^a and activity^b of skeletal muscle LPL.





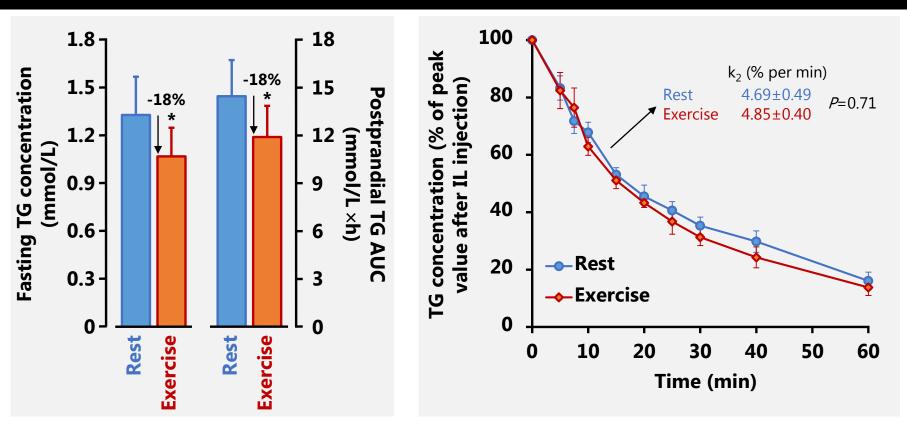
^a7 men (age ~28 yr, BMI ~22 kg/m²) cycled for 120 min at 60% VO_2 peak (left); ^b8 men (age ~27 yr, BMI ~24.5 kg/m²) cycled for 90 min at 60% VO_2 peak (right). Subjects were healthy and recreationally active but untrained. Plasma TG and skeletal muscle LPL were assessed the day after a single bout of exercise (12–24 h post-exercise).

Ο ρυθμός κάθαρσης TG αυξάνει μετά από πολύ άσκηση άλλα όχι μετά από λιγότερη, παρά τις μειωμένες [TG]



10 normally active men (aged 28 ± 1 years, BMI 22 ± 1 kg/m², Wmax 258 ± 11 watt) performed a single 1.5-hr or 3-hr bout of endurance exercise (interchanging 60 min running / 30 min cycling) at moderate intensity (77% of HRmax), in random order 4-6 weeks apart; IVFTTs (10% Intralipid; 1 ml/kg BW) were performed one day before, immediately before, immediately after, one day after, and (for the 3-hr trial) two and three days after the exercise bout, always in the fasted state. First-order TG clearance constants (k_2) were calculated.

Η υποτριγλυκεριδαιμία της άσκησης μπορεί να εμφανιστεί απουσία αυξημένης κάθαρσης TG



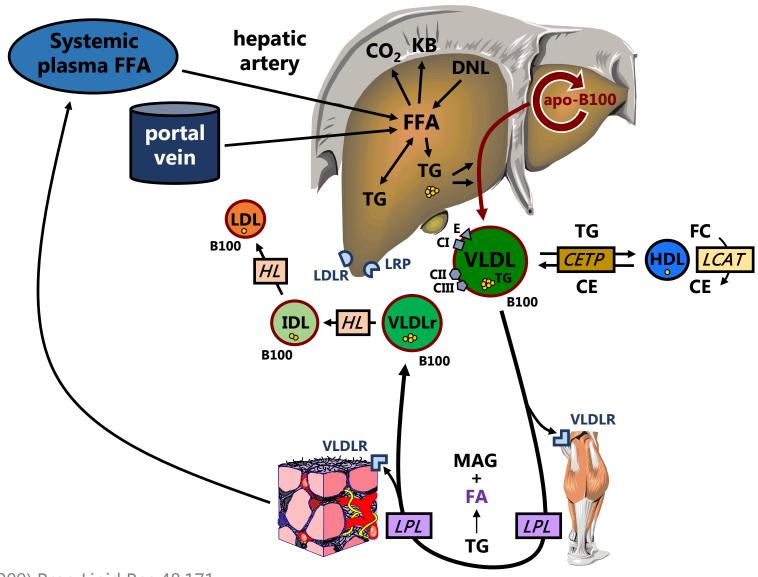
8 healthy men (aged 48.3 ± 2.6 years, BMI 25.5 ± 1.0 kg/m², VO₂max 39.0 ± 2.2 ml/kg·min) participated in two intravenous fat tolerance tests (20% Intralipid; 0.5 ml/kg BW—0.1 g fat/kg), in random order separated by 5 days. On the previous afternoon, they completed 90 minutes of exercise at moderate intensity (walking, jogging or running on a treadmill at 60% of VO₂max), or an equivalent period of rest. First-order TG clearance constants (k₂) were calculated from post-Intralipid TG concentrations (after subtraction of fasting values) by fitting mono-exponential regression lines to the TG clearance curves (i.e. the first 20 or 25 min of the IVFTT, depending on the subject).

Ομοιόσταση των VLDL-TG: η απλή εικόνα

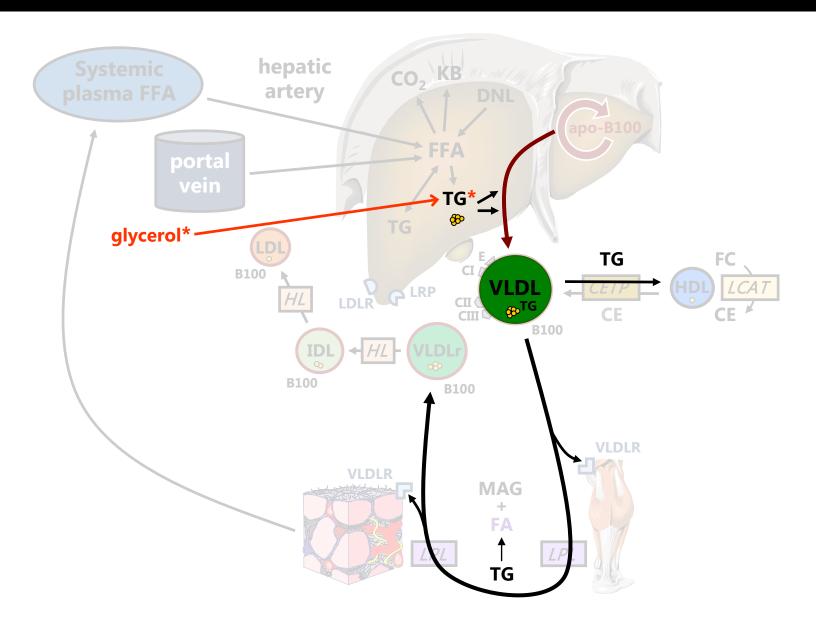


When the concentration in the bloodstream is constant (e.g. in the postabsorptive state), the rate of influx must equal the rate of efflux.

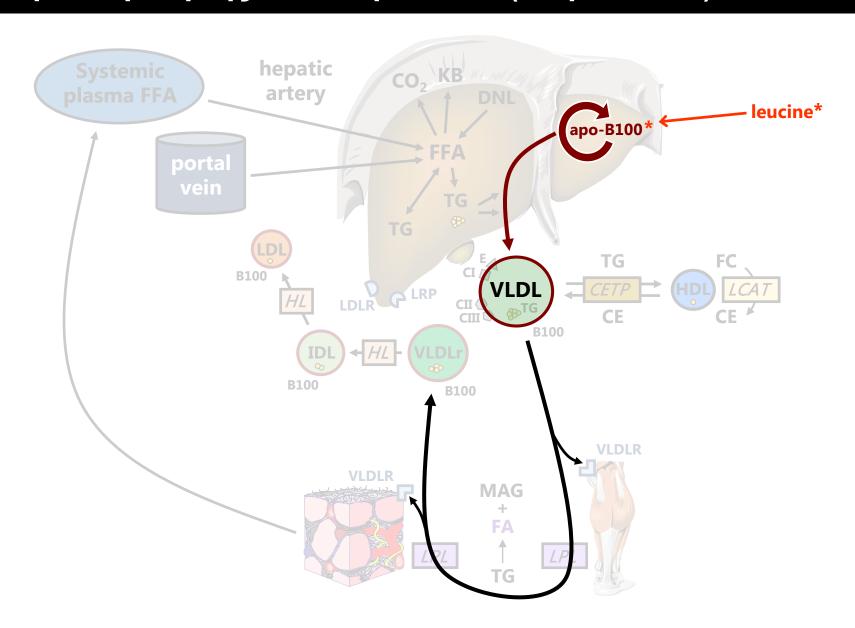
Μεταβολισμός των VLDL-TG: η όχι-και-τόσο-απλή εικόνα



Μεταβολισμός των VLDL: η χρήση σεσημασμένης γλυκερόλης για την κινητική των VLDL-TG *in vivo*

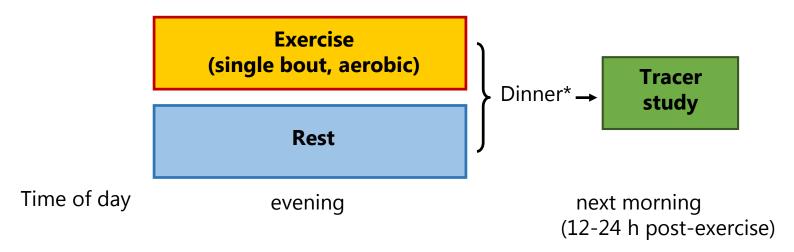


Μεταβολισμός των VLDL: η χρήση σεσημασμένης λευκίνης για την κινητική της VLDL-apoB-100 (σωματιδίων) *in vivo*



Πειραματικό πρωτόκολλο για τη μελέτη της άσκησης στην κινητική των VLDL

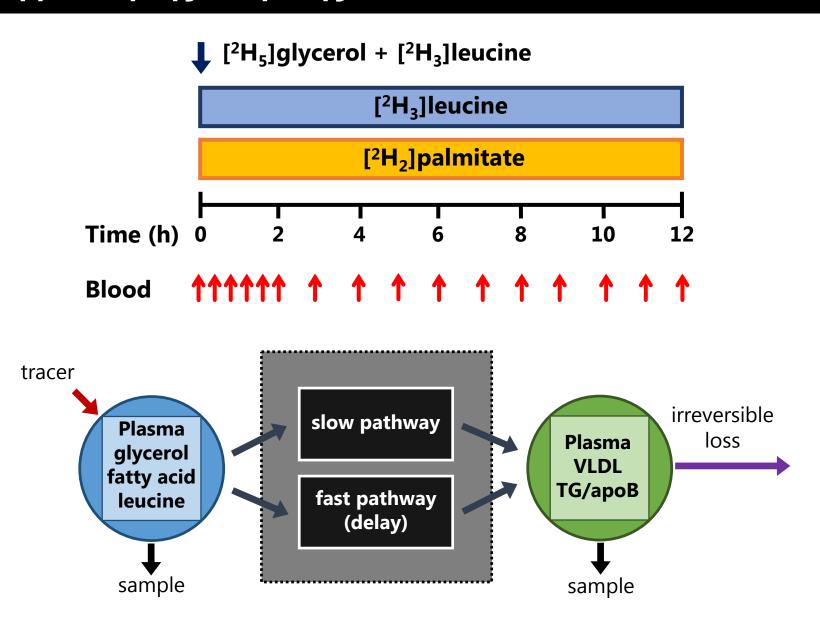
Paired cross-over design with time-matched trials



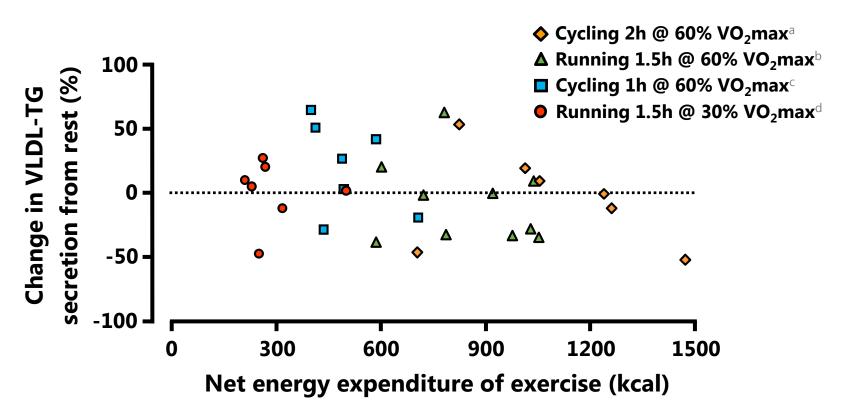
Apparently healthy, untrained, non-obese men and women

^{*} Low fat mixed meal (note: basal hypotriglyceridemia the next morning is not the end-result of exercise-induced reduction in postprandial lipemia after dinner)

Πρωτόκολλο έγχυσης ισοτόπων και μαθηματικό μοντέλο για τη μελέτη της κινητικής των VLDL

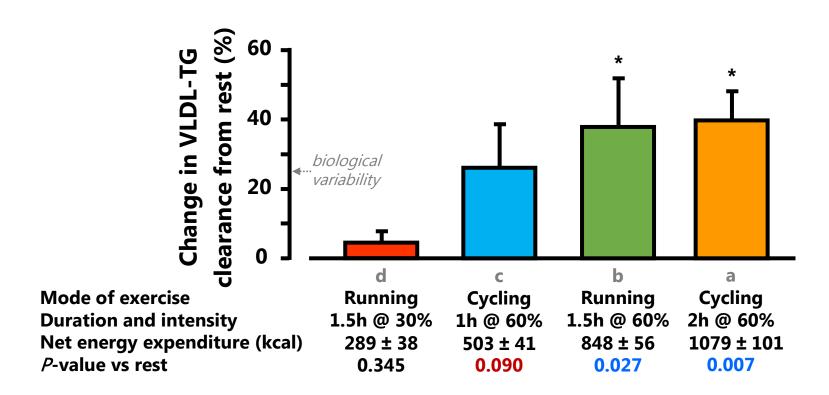


Η αερόβια άσκηση δεν επηρεάζει το ρυθμό έκκρισης VLDL-ΤG από το ήπαρ



^a7 men (age ~28 yr, BMI ~22 kg/m²) cycled for 2 h at moderate intensity; ^b10 men (age ~26 yr, BMI ~25 kg/m²) ran for 1.5 h at moderate intensity; ^c7 men (age ~30 yr, BMI ~23 kg/m²) cycled for 1 h at moderate intensity; ^d7 men (age ~25 yr, BMI ~24 kg/m²) walked for 1.5 h at low intensity. Subjects were healthy and recreationally active but untrained. VLDL kinetics were assessed the day after a single bout of exercise (12−24 h post-exercise).

Η αερόβια άσκηση αυξάνει το ρυθμό κάθαρσης VLDL-TG με τρόπο rise-to-plateau

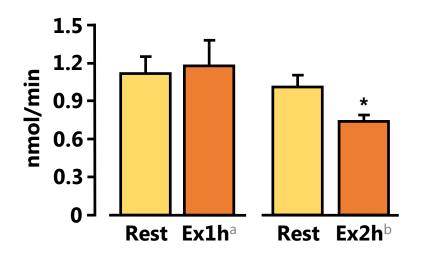


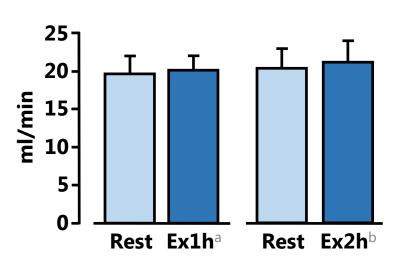
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Η αερόβια άσκηση μειώνει το ρυθμό έκκρισης VLDL-apoB-100 (δηλ. VLDL σωματιδίων) από το ήπαρ

Secretion of VLDL-apo-B100 from the liver

Clearance of VLDL-apo-B100 from the circulation

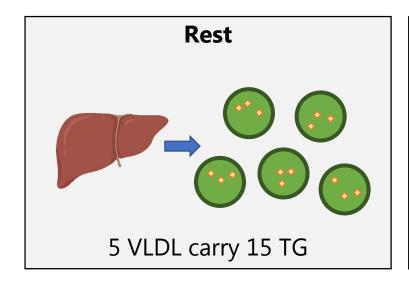


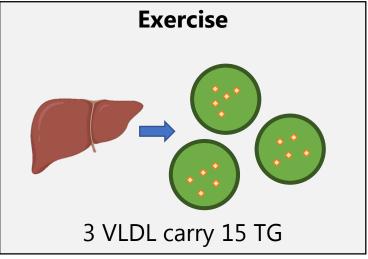


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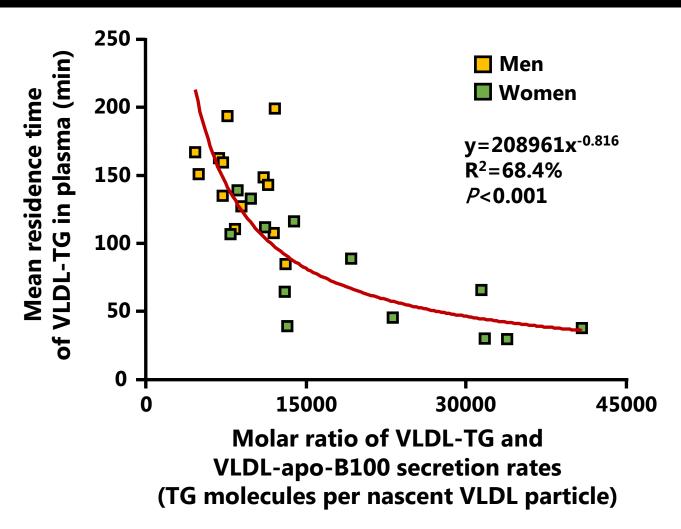
Το γεγονός-κλειδί μετά την αερόβια άσκηση

The liver after exercise secretes the same number of TG in fewer VLDL particles than after rest, hence it packs more TG per VLDL particle. This means that it secretes TG-richer and thus also larger VLDL particles!





Ο ρυθμός απομάκρυνσης TG από τον πυρήνα μεγαλύτερων και πλουσιότερων σε TG VLDL είναι ταχύτερος



Basal VLDL kinetics were assessed in 26 healthy lean subjects (13 men and 13 women) matched for age (~29 yr) and BMI (~22 kg/m²).

Μηχανιστικό μοντέλο της υποτριγλυκεριδαιμίας της άσκησης 1.0

Reduced hepatic VLDL-apoB-100 secretion (fewer particles)

Secretion of larger and TG-richer nascent VLDL

Accelerated whole-body LPL-mediated clearance of VLDL-TG

Reduced plasma TG concentration

Exercise-induced hypotriglyceridemia is the net result of **changes in lipid metabolism in the periphery** (increased VLDL-TG clearance rate), which are not driven by changes in skeletal muscle LPL activity but rather, are **initiated by remote changes in protein metabolism in the liver** (decreased VLDL-apoB-100 secretion rate). This highlights not only the interaction between lipid and protein metabolism, but also the co-operation and co-ordination of different organs in the integration and regulation of metabolism at the whole-body level in humans.

Πως μειώνει η άσκηση την παραγωγή VLDL-apoB-100 από το ήπαρ;

Increased insulin sensitivity (muscle+liver)

Devlin (1987) Diabetes 36:434 Mikines (1988) Am J Physiol 254:E248

In humans, acute hyperinsulinemia decreases hepatic VLDL-apoB-100 secretion

Lewis (1995) J Clin Invest 95:158

So, increased insulin action on the liver the day after exercise may be responsible for the decrease in hepatic VLDL-apoB-100 secretion rate.

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So, increased insulin action on the liver the day after exercise may be responsible for the decrease in hepatic VLDL-apoB-100 secretion rate.

. . .

But then again, insulin also inhibits VLDL-TG secretion from the liver in animals and humans, thus improved hepatic insulin sensitivity alone cannot explain the exercise-induced changes in VLDL-TG metabolism.

Μηχανιστικό μοντέλο της υποτριγλυκεριδαιμίας της άσκησης 1.1

Unchanged hepatic VLDL-TG secretion



Reduced hepatic VLDL-apoB-100 secretion (fewer particles)



Secretion of larger and TG-richer nascent VLDL



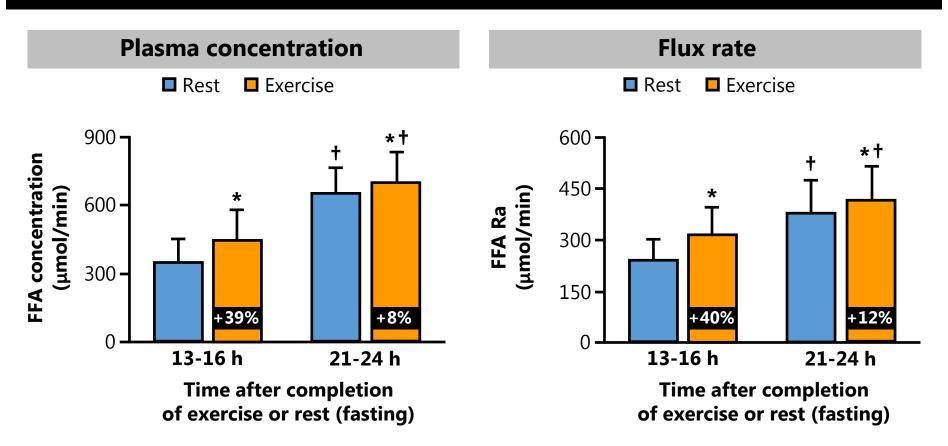
Accelerated whole-body LPL-mediated clearance of VLDL-TG



Reduced plasma TG concentration

Γιατί δε μειώνει η άσκηση και την παραγωγή VLDL-TG;

Η αερόβια άσκηση αυξάνει τη διαθεσιμότητα ελευθέρων λιπαρών οξέων την επόμενη ημέρα

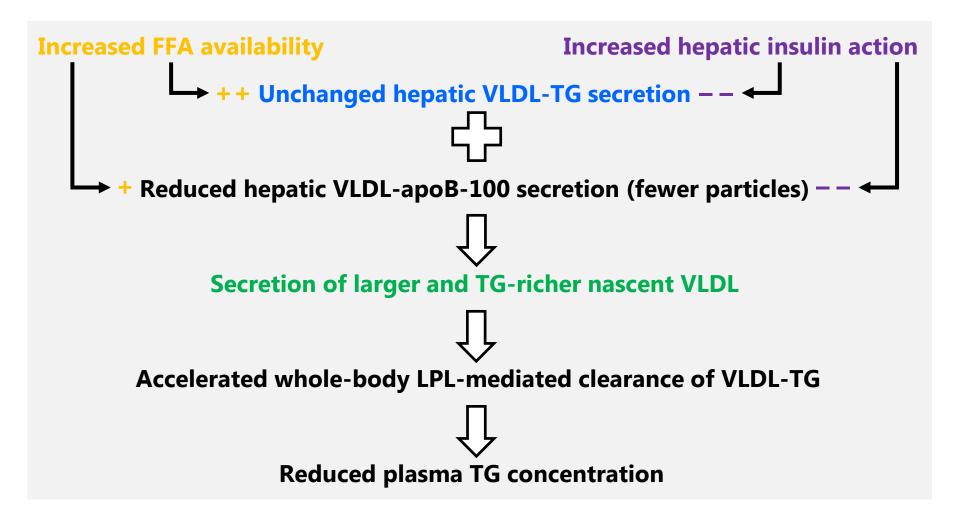


Stable isotope-labeled palmitate infusion ($[2,2^{-2}H_2]$ palmitate for 12 hours) was used to examine free fatty acid metabolism in 27 healthy untrained men and women (aged 28.9±1.4 years; BMI 24.7±0.8 kg/m²) between 13-16 hours and 21-24 hours after a single bout of moderate-intensity endurance exercise (1 or 2 hours of cycling at 60% of VO₂max) performed in the previous evening, and after a time-matched resting trial (in random order, approximately 4 wk apart).

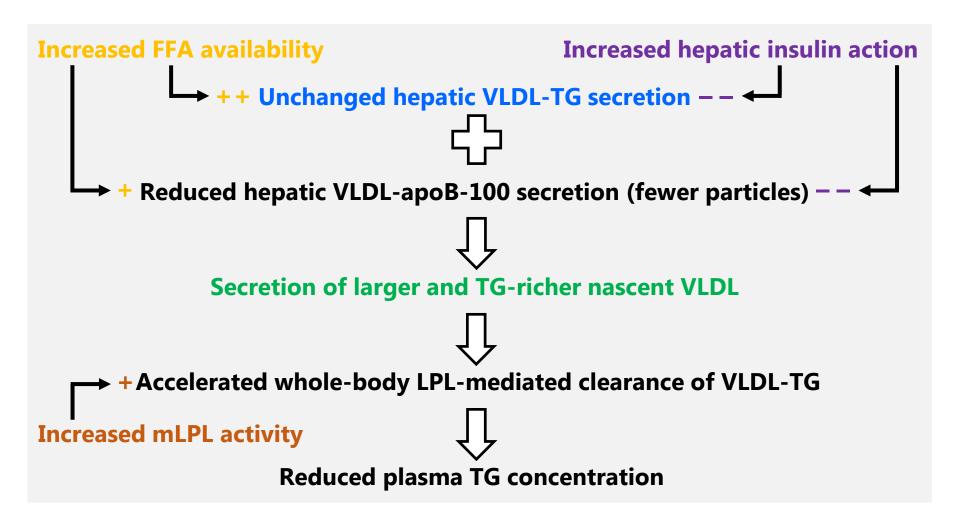
Δράση της ινσουλίνης και των FFA στους ρυθμούς παραγωγής VLDL-TG και VLDL-apoB-100 *in vivo*

	VLDL-TG secretion	VLDL-apoB-100 secretion
Insulin alone	$\downarrow\downarrow$	$\downarrow\downarrow$
FFA alone	$\uparrow \uparrow$	↑

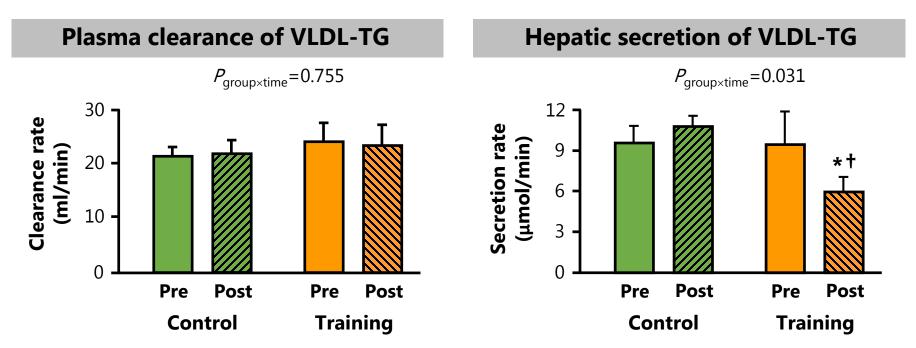
Μηχανιστικό μοντέλο της υποτριγλυκεριδαιμίας της άσκησης 2.0



Μηχανιστικό μοντέλο της υποτριγλυκεριδαιμίας της άσκησης 2.1



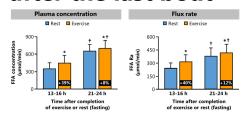
Η χρόνια αερόβια άσκηση (προπόνηση) μειώνει τα TG λόγω μειωμένης έκκρισης VLDL-TG



Healthy untrained men were randomly assigned to a **non-exercising control** group (n=8) or an **exercise training** group (n=8; 1 dropout). Training involved 2 months of supervised high-intensity interval exercise (3 sessions/wk; running at 60|90% of VO_2 max in 4-min intervals for a total of 32 min; gross energy expenditure: 446 ± 29 kcal). VLDL-TG kinetics were measured in the basal postabsorptive state before and after the intervention (**~48 h after the last exercise bout** in the training group). Training decreased fasting plasma VLDL-TG concentration by 28% and increased VO_2 max by ~18% (both P<0.05), but did not alter body weight and body composition and did not affect **fasting FFA concentration**. No significant changes in VLDL-TG concentration and kinetics occurred in the non-exercising control group.

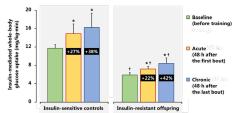
Αερόβια προπόνηση και ινσουλινο-ευαισθησία, διαθεσιμότητα FFA και κινητική VLDL-apoB-100

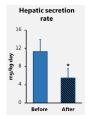
Aerobic training does not affect basal plasma FFA availability 36-72 hrs after the last bout



Sial (1998) Am J Physiol Endocrinol Metab 274:E785 Horowitz (1999) Am J Physiol Endocrinol Metab 277:E325 Horowitz (2000) Am J Physiol Endocrinol Metab 279:E348 Friedlander (1998) Am J Physiol Endocrinol Metab 275:E853 Friedlander (1999) J Appl Physiol 86:2097

Aerobic training increases whole-body insulin sensitivity (muscle and probably also liver) 36-72 hrs after the last bout



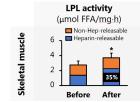


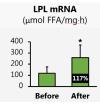
Perseghin (1996) N Engl J Med 335:1357 Burstein (1985) Diabetes 34:756 Mikines (1988) Am J Physiol 254:E248 Steenberg (2019) J Physiol 597:89 Ross (2000) Ann Intern Med 133:92

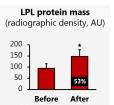
Aerobic training decreases hepatic VLDL-apoB-100 secretion rate 72 hrs after the last bout

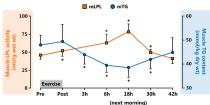
Alam (2004) J Clin Endocrinol Metab 89:688

Aerobic training increases muscle LPL activity only when measured within 24 hrs from the last bout



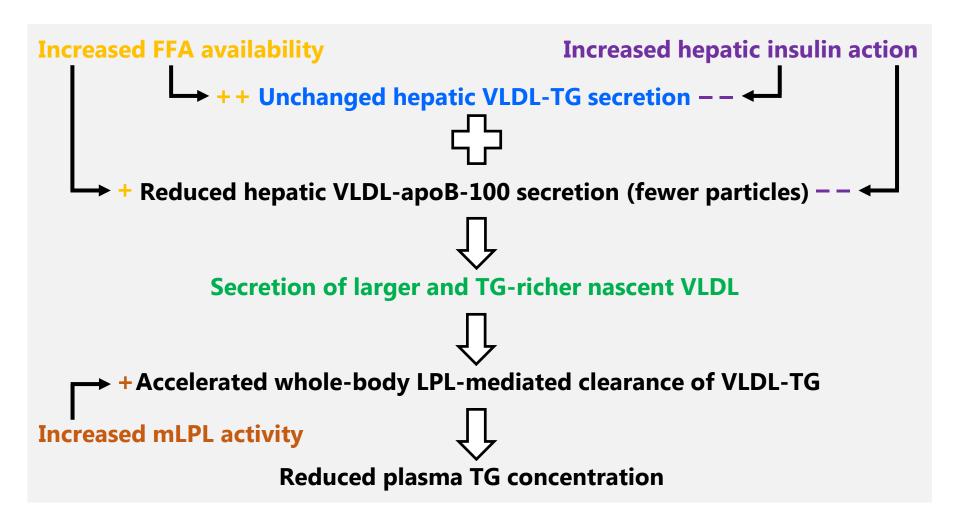




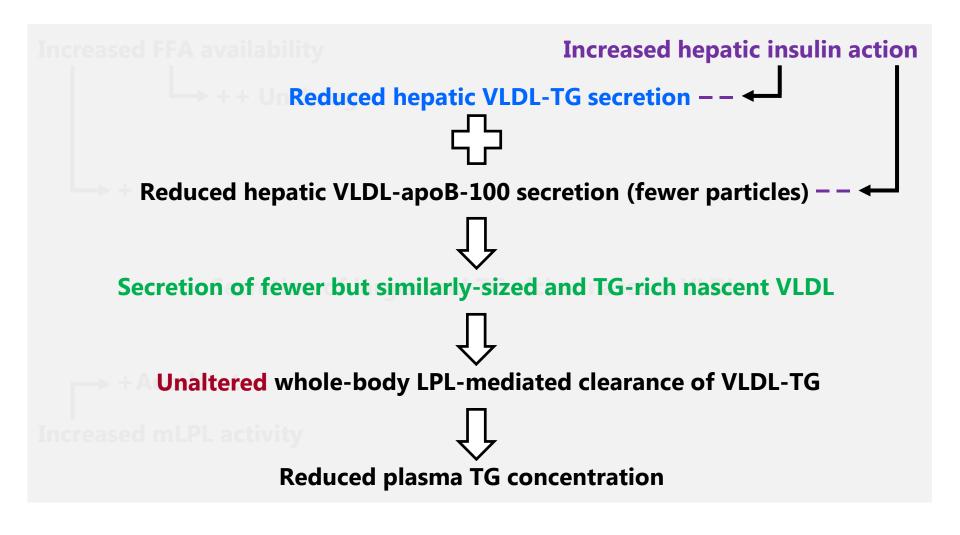


Seip (1995) Am J Physiol 268:E229 Nikkila (1978) Metabolism 27:1661

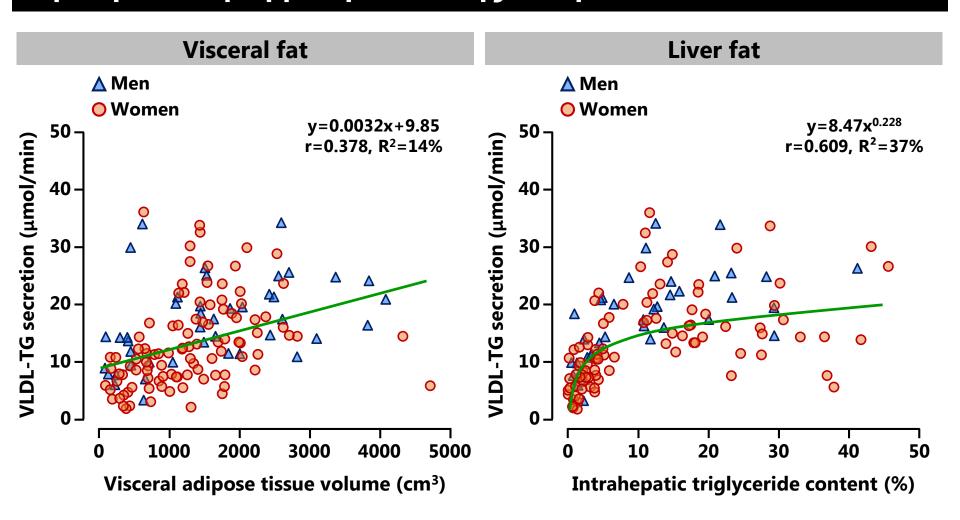
Μηχανιστικό μοντέλο της υποτριγλυκεριδαιμίας της άσκησης 2.1



Μηχανιστικό μοντέλο της υποτριγλυκεριδαιμίας της άσκησης 2.1plus



Αλλαγές στο σπλαχνικό και ενδοηπατικό λίπος μετά από την προπόνηση μπορεί επίσης να εμπλέκονται



Basal VLDL-triglyceride kinetics (12-h tracer infusion), VAT volume (MRI) and IHTG content (MRS) were assessed in 233 men (n=89) and women (n=144), aged 18–55 years, with a BMI of $19-45 \text{ kg/m}^2$.

Περίληψη: οι μηχανισμοί της υποτριγλυκεριδαιμίας της άσκησης

- Μία συνεδρία αερόβιας άσκησης σε μέτρια ένταση μειώνει τη συγκέντρωση
 ΤG την επόμενη ημέρα λόγω επιταχυμένου ρυθμού απομάκρυνσης VLDL-TG
 από ολόκληρο το σώμα.
- Η επιτάχυνση του ρυθμού απομάκρυνσης των VLDL-TG οφείλεται στην έκκριση από το ήπαρ λιγότερων VLDL αλλά μεγαλύτερων σε μέγεθος και πλουσιότερων σε περιεκτικότητα σε TG.
- Οι αλλαγές στη δράση (και στη συγκέντρωση) ινσουλίνης, στη διαθεσιμότητα FFA, αλλά και στη δραστικότητα της LPL στο μυ εμπλέκονται στο μεταβολισμό των VLDL ανάλογα με την «ποσότητα» της άσκησης και τη χρονική διάρκεια από το τέλος της άσκησης.
- Η αερόβια προπόνηση μειώνει τη συγκέντρωση ΤG λόγω επιβραδυμένου ρυθμού έκκρισης VLDL-TG από το ήπαρ. Πιθανοί λόγοι: απουσία αυξημένης διαθεσιμότητας FFA σε συνδυασμό με αυξημένη ινσουλινοευαισθησία και πιθανόν η ελάττωση του σπλαχνικού και του ενδοηπατικού λίπους.

