A nutrient cocktail prevents the deterioration in lipid metabolism induced by 20 days of daily steps reduction and fructose overfeeding

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Abstract

PURPOSE: Physical inactivity and sedentary behaviours are recognized as major independent risks factors for numerous diseases. We examined the capacity of a nutrient cocktail composed of polyphenols, omega-3 fatty acids, vitamin E and selenium to prevent the metabolic deteriorations induced by 20 days of step reduction, including fructose overfeeding during the last 10 days.
METHODS: 20 healthy trained men (14000 steps per day and engaged in sports) were randomly divided into a control group (no supplementation) and a cocktail group for a 20-day free-living intervention during which they decreased their daily steps to 3000 per day. On days 0, 10 and 20 we measured body composition, blood chemistry, glucose tolerance and substrate oxidation. Glucose tolerance included 1% fructose labelled with (U-13C) fructose to assess liver *de novo* lipogenesis. On days 0 and 20, muscle biopsies were performed to assess cellular mechanisms.
RESULTS: While the cocktail did not prevent deterioration of insulin sensitivity and its muscular correlates, it fully prevented the hypertriglyceridemia, the drop in fasting HDL and total fat oxidation as well as the increase in *de novo* lipogenesis, as assessed from both (U-13C) fructose and indirect calorimetry. Furthermore, the cocktail prevented a decrease in muscle cross-sectional area and was associated with lower protein ubiquitination and BCL2 content.
CONCLUSION: A cocktail of nutrient compounds from dietary origin protect against the deterioration in lipid metabolism induced by physical inactivity and fructose overfeeding.

Introduction

- Sedentarity has taken a more important part in our societies over the last decades.
- Epidemiological evidences point towards a clear role of physical inactivity and sedentarity behaviours in numerous disease risks such as Type 2 Diabetes, Insulin resistance or obesity[1].
- Functional disabilities ensue such as a loss of muscular strength and volume, with a shift in muscular fibers from oxidative to glycolytic muscle fibers.
- Osteoporosis, cardiovascular and metabolic deteriorations are also recognized.
- The physiological mechanisms need to be better understood.
- Space researches tested different countermeasures to counteract physiological alterations caused by physical inactivity, but so far, none have proved to be fully effective[2].
- Interest is now focused on micronutrients, vitamins and bio-active compounds with additive effects when taken as a cocktail[3].

GOAL

- To assess the metabolic deteriorations induced by physical inactivity
- To counteract physiological adaptations by the ingestion of daily dietary cocktail supplementation

References
[1] Mazzucco, S. et al. (2010) Clin Nutr 29(3): 386-390. [2] Ploutz-Snyder L. (2016) J Appl Physiol: 915-21.
[3] Hargens, A. R. et al. (2016) J Nutr Sci Vitaminol (Tokyo) 59(4): 317-324

Subjects & Methods

SUBJECTS

- 20 healthy trained young men (>15000 steps/day during a week).

STUDY DESIGN

- Randomized in CONTROL (n=10) and SUPPLEMENTED (n=10) group over the 20-day period of the protocol in free living conditions.
- No exercises and drastic decrease of daily physical activity controlled through a Fitbit pedometer.
- Subjects came to the site of investigation (MEDES Space Clinic, Toulouse) on days 0,10 and 20.
- Metabolic degradation induced by physical inactivity was boosted by the consumption of daily 3g/kg/d of Fructose for the last ten days of the study.

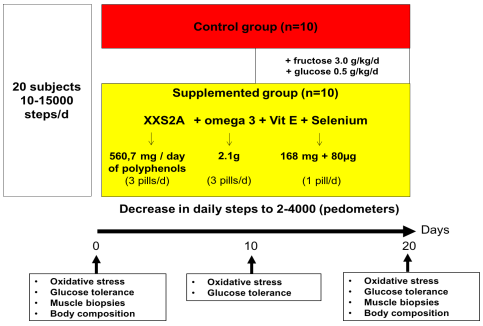

Figure 1: Design of enforced reduced physical activity protocol and details of daily cocktail supplementation.

MEASUREMENTS

- DEXA analysis to measure body composition such as fat-mass and lean-body-mass.
- A four-hour OGTT (1g/kg of glucose and 0.5g/kg of fructose with 1% of fructose as $U^{13}C_6$ Fructose) to assess glucose tolerance, insulin sensitivity and lipogenesis from fructose.
- Breath samples collected to assess $U^{13}C_6$ fructose oxidation.
- Indirect calorimetry every 30 minutes to determine energy expenditure and substrate oxidation.
- Fasting blood collection to evaluate inflammation, oxidative stress.
- Blood samples realised over the OGTT to estimate VLDL-triglyceride concentration.
- Biopsies performed on days 0 and 20 on *Vastus Lateralis* to assess muscular evolution.
- **STATISTICAL ANALYSIS**
- Mixed linear models with group, intervention, group-by-intervention interaction and baseline values as fixed effects and individuals as random effects.
- Significance was set up at $p < 0.05$ for main effects and $p < 0.10$ for interaction effects.
- Comparison between groups are presented adjusted on baseline or adjusted on both baseline and fat mass (FM) and fat free mass (FFM).
- Post-hoc tests used to assess the effect of intervention between groups at the different visits.
- Significative differences between cocktail and control groups are presented as p<0.05(*), p<0.01(**), p<0.001(***).

Results

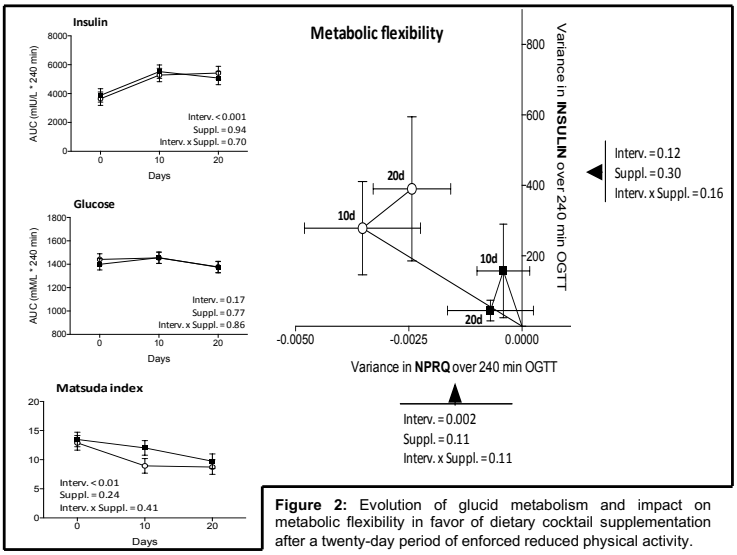

Figure 2: Evolution of glucid metabolism and impact on metabolic flexibility in favor of dietary cocktail supplementation after a twenty-day period of enforced reduced physical activity.

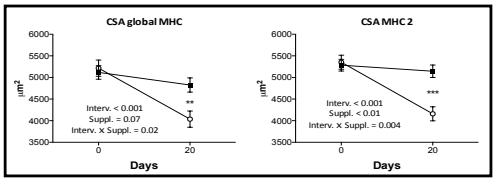

Figure 3: Evolution of Myosin Heavy Chain (global and II) cross sectional areas after *V. lateralis* biopsies.

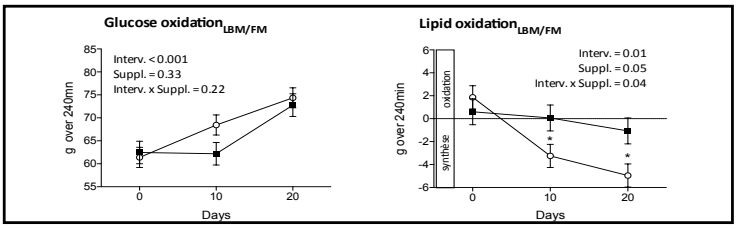

Figure 4: Evolution of both glucose and lipid oxidation based on indirect calorimetry measurements.

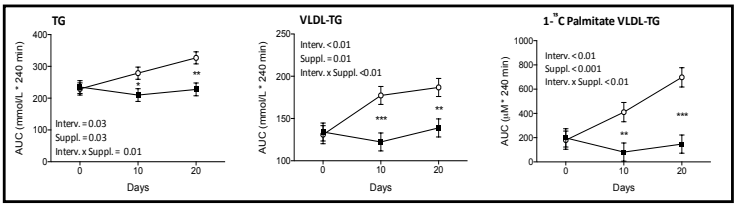

Figure 5: Evolution of both plasma triglycerides, triglycerides from ultracentrifuge-separated-VLDL, and 1-^{13}C Palmitate enrichment from VLDL analysed by GC-MS.

Mixed model:
Interv. : Physical inactivity & Fructose / Glucose intake
Suppl. : Cocktail supplementation
Post hoc:
* p < 0.05, ** p < 0.01, *** p < 0.001
Control vs Supplemented at each time

Control
Supplemented

Summary & Conclusions

CONCLUSION: While insulin and glucose responses were only modestly affected in the two groups, supplemented group exerted higher metabolic flexibility in comparison to control group which witnessed the development of insulin resistance (Figure 2).
Twenty days of enforced reduced physical activity decreased by 20% total and type-2-myosin heavy chain cross sectional areas in the control group, that was prevented in the supplemented group (Figure 3).
Indirect calorimetry data tends to demonstrate a reduced lipid oxidation that was partially counteracted by dietary cocktail supplementation (Figure 4).
Moreover, the cocktail counteracted the deterioration of lipid metabolism induced by the twenty-day deconditioning period as shown on both plasma and VLDL-sorted triglycerides analysed by GC-MS (Figure 5).
The anti-oxidant dietary cocktail supplementation showed promising results with number of scientific and clinical implications for both general population and hospitalized bed rest patients.

Dietary cocktail supplementation partially counteract muscular and metabolic alterations but diet-control long-term investigations are required to better understand the mechanisms involved in development of insulin resistance and ectopic fat storage.