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LETTER TO THE EDITOR Open Access

Revisiting the effect of acute intermittent hypoxemia on postprandial triglyceride levels in healthy young men

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Dear editor,

Obstructive sleep apnea is a breathing disorder characterized by brief and repeated obstructions of the upper respiratory airway during sleep, resulting in transient reductions in oxyhemoglobin saturation, known as intermittent hypoxemia. The increasing global prevalence of obstructive sleep apnea raises concerns due to its associations with various comorbidities and the resulting strain on health systems [1]. A key link between OSA and the development of metabolic diseases may involve dysregulated lipid metabolism, particularly in men [2]. Our previous reports aimed to elucidate this link by examining changes in postprandial lipid levels following the consumption of a high-fat meal during an acute bout of intermittent hypoxemia simulating moderate obstructive sleep apnea in individuals living without the breathing disorder, compared to a control normoxia condition.

Initially, we found that intermittent hypoxemia had no statistically significant effect on postprandial triglyceride levels in healthy young men [3]. Subsequently, in another cohort of healthy young men undergoing the same experimental conditions, we observed a tendency for intermittent hypoxemia to increase postprandial triglyceride levels, including buoyant triglyceride-rich lipoprotein triglyceride (TRL-TG) predominantly composed of chylomicrons; however, these elevations were not statistically significant [4]. Most recently, when comparing blood lipid levels during intermittent hypoxemia between women and men, we found that intermittent hypoxemia led to statistically significantly higher levels of total triglycerides, denser TRL-TG predominantly composed of very low-density lipoprotein and chylomicron remnants, and buoyant TRL-TG in men only [5].

We attribute part of the discrepancy between our recent findings and the two initial studies to the statistical approach employed. Specifically, the initial studies employed a repeated measures analysis of variance, which, compared to linear mixed-effects models, represents a less robust analysis partly due to the loss of degrees of freedom for each repeated measurement. Consequently, we revisited these initial studies by re-analyzing their combined dataset using the linear mixed-effects model approach. This approach is particularly helpful as it allows for the simultaneous incorporation of fixed effects (e.g., time) and random effects (e.g., participant-specific intercepts), accounting for various sources of variability within the data.

Our methodological design employed a laboratory-based randomized crossover trial where participants (n=18 healthy young men; mean [SD]: 23 [3] years, 84.4 [10.7] kg, 25.4 [3.5] kg/m^2) were exposed to six hours of normoxia (ambient air: fraction of inspired

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Table 1 Fasting parameters per experimental condition

	Normoxia	Intermittent Hypoxemia	*p*-value
Total triglycerides (mmol/L)	1.1 (0.4)	1.2 (0.7)	0.547
Denser TRL-TG (mmol/L)	1.1 (0.3)	1.5 (0.9)	0.393
Buoyant TRL-TG (mmol/L)	0.08 (0.0)	0.15 (0.1)	0.271
Non-esterified fatty acids (mmol/L)	0.4 (0.2)	0.4 (0.2)	0.306
Glucose (mmol/L)	4.5 (0.6)	4.8 (0.6)	0.024
Insulin (pmol/L)	24.0 (35.5)	28.0 (34.1)	0.648

Note data are presented as mean (SD) and were compared using Student's paired two-tailed *t* tests. Denser TRL-TG and buoyant TRL-TG represent a subset of participants ($n=8/18$)

oxygen=0.2098, ~98% oxyhemoglobin saturation) or intermittent hypoxemia (~15 hypoxemic cycles per hour: 100% medical-grade nitrogen, ~85% oxyhemoglobin saturation) following the consumption of a high-fat meal (33% of estimated daily energy expenditure; 59% of calories from fats, 31% from carbohydrates, and 10% from proteins) [3, 4]. Venous blood samples were collected repeatedly after meal consumption and plasma levels of total triglycerides, denser TRL-TG, buoyant TRL-TG, non-esterified fatty acids (NEFA), glucose, and insulin were measured as previously described [5].

Student's paired two-tailed *t* tests were used to compare fasting parameters between conditions (normoxia, intermittent hypoxemia). All other variables were analyzed using linear mixed-effects models to evaluate the effects of time and condition with Bonferroni correction, while participant identification was modelled as a random effect. Data for denser and buoyant TRL-TG levels were analyzed with a reduced sample size (both $n=8$) as they were not isolated in one of the initial studies. Statistical analyses were conducted using *jamovi* (v.2.2.5, with the *gamlj* module, v.2.6.6) and an alpha of 0.050. Figures were created using GraphPad Prism (v.10.2.2).

There was no difference in fasting parameters between conditions (all $p\geq0.271$; Table 1), except for fasting glucose ($p=0.024$); however, glycemia was within the normal range for fasting values in both conditions. Compared to normoxia, intermittent hypoxemia led to higher postprandial levels of total triglycerides, denser TRL-TG, buoyant TRL-TG, NEFA, and glucose (main effect of condition: all $p\leq0.013$; Fig. 1), despite similar insulin levels (main effect of condition: $p=0.678$; Fig. 1). The main effect of condition for glucose remained statistically significant even after an additional adjustment for baseline values by including fasting glucose as a covariate in the statistical model (main effect of condition: $p=0.002$). On average, two hours after consuming the high-fat meal under intermittent hypoxemia, total triglycerides were ~14% higher than normoxia, denser TRL-TG were ~25% higher, buoyant TRL-TG were ~49% higher, and glucose was ~14% higher. NEFA were ~29% higher following 6 h of intermittent hypoxemia.

In summary, by using a more robust statistical approach than our previous reports, we demonstrated that, following a high-fat meal, intermittent hypoxemia leads to higher levels of total triglycerides, denser TRL-TG, buoyant TRL-TG, NEFA, and glucose in healthy young men when compared to normoxia. This occurred despite similar insulin levels across conditions. Notably, our findings are limited to the specific simulated model of obstructive sleep apnea employed. Future studies with more ecological designs are needed to better understand how intermittent hypoxemia leads to dysregulated lipid metabolism in humans.

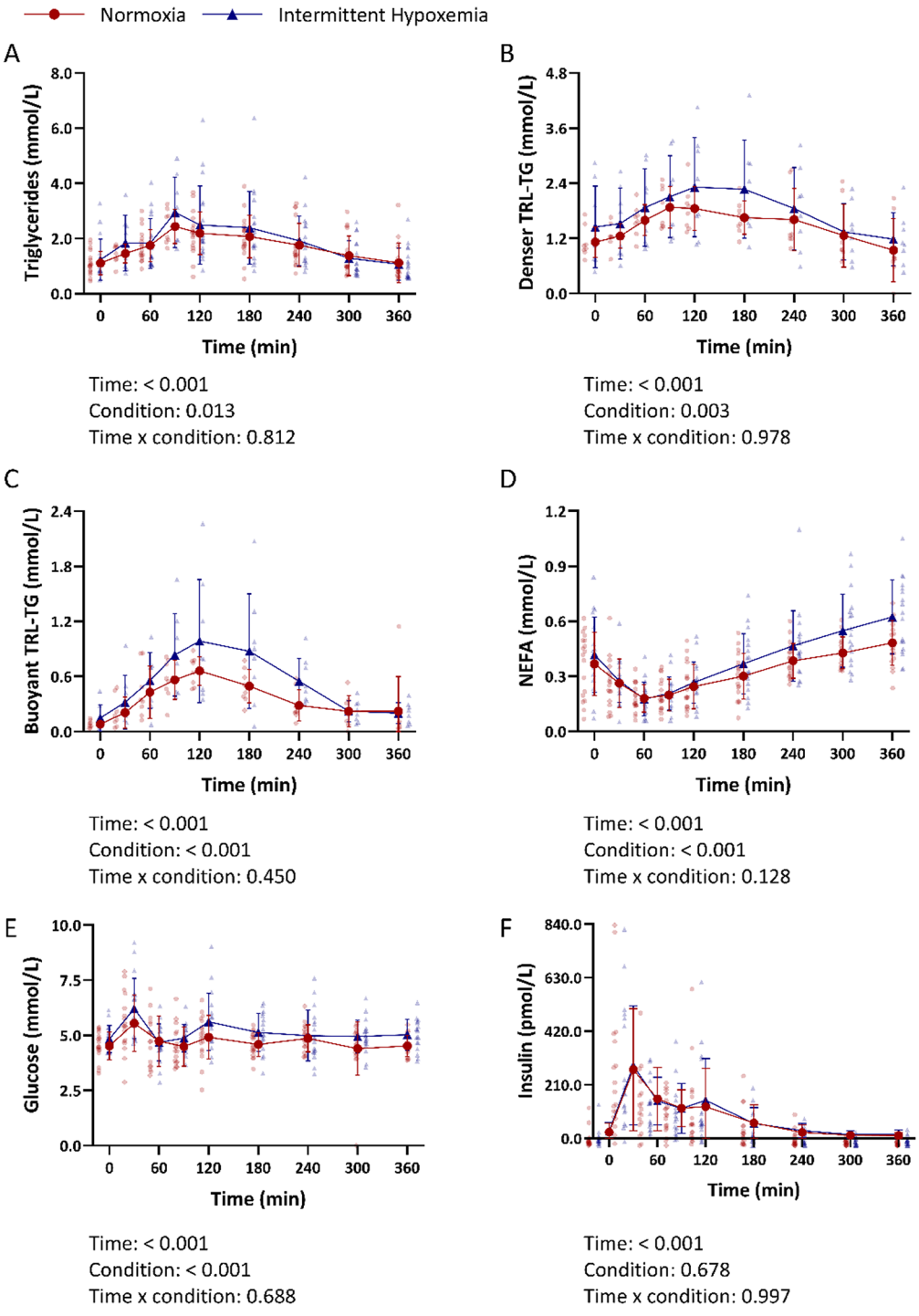

Fig. 1 Plasma levels of total triglycerides (**A**), denser TRL-TG (**B**), buoyant TRL-TG (**C**), non-esterified fatty acids (**D**), glucose (**E**), and insulin (**F**) over six hours of normoxia and intermittent hypoxemia at baseline and following a high-fat meal in healthy young men. Data are presented as mean (SD) and individual points, and were analyzed using linear mixed-effects models

Abbreviations
TRL-TG Triglyceride-rich lipoprotein triglycerides

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Author contributions
All persons designated as authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship, and all those who qualify are listed. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Conceptualization: PI; Formal analysis: NG; Funding acquisition: RA, PI; Investigation: NG, RM, JFM; Methodology: NG, RM, JFM, PI; Supervision: PI; Visualization: NG; Writing – original draft: NG; Writing – review & editing: RM, JFM, RA, PI.

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Data availability
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
All individuals provided written informed consent before participation. The study protocol was approved by the Research Ethics Boards of the University of Ottawa and Hôpital Montfort.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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