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TITLE: Interrupting Sitting Time with Simple Resistance Activities Lowers Postprandial Insulinemia in Adults with Overweight/Obesity

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RUNNING TITLE: Interrupting Sitting with Resistance Activities

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AUTHOR CONTRIBUTIONS: DWD, DG, BAK, NO, MG, RL, PD and NC were involved in the concept and design of the study. HA, NC, RL and MG were involved in participant recruitment, data collection and ensured that the trial was conducted in accordance with approved protocols. FD was responsible for the statistical analysis of the data. RL wrote the manuscript and PD, NO, and DWD helped revise the manuscript for important intellectual content. Final manuscript revisions were made by DG, BAK, MG and NC and all authors provided final approval for the work to be published. DWD takes full responsibility for the study as a whole, including the integrity of the data and study design, permission to access data and the decision to submit and publish the manuscript.

STUDY IMPORTANCE:

- Interrupting sitting time with brief bouts of bodyweight resistance exercises (simple resistance activities) improves postprandial metabolism in those with type 2 diabetes, but the effects in adults without diabetes are unknown.

- This manuscript reports findings of a randomized, crossover trial in which regularly interrupting sitting time with simple resistance activities lowered postprandial hyperinsulinemia, but not postprandial glucose responses, in adults with overweight/obesity.

- Given that hyperinsulinemia has been implicated in the development of chronic diseases such as type 2 diabetes and cardiovascular disease, interrupting sitting with regular short bouts of simple resistance activities may offer a potential approach to managing cardiometabolic risk in adults with overweight/obesity.

ABSTRACT (199 words)

Objective: To examine the effects on postprandial glucose and insulin responses of interrupting sitting time with brief bouts of simple resistance activities (SRAs) in adults with overweight/obesity.

Methods: Participants (n=19) were recruited for a randomized crossover trial involving two 6-hour conditions: 1) uninterrupted sitting, or 2) sitting with 3-minute bouts of SRAs (half-squats, calf raises, gluteal contractions and knee raises) every 30 minutes (total duration=27 minutes). Incremental areas-under-the-curve (iAUC) for glucose, insulin and insulin:glucose ratio were analyzed as pre-specified secondary outcomes using mixed-effects log-linear regression adjusted for sex, body mass index, treatment order and pre-prandial values. Results are reported as multiplicative change [exponentiated coefficient (EC) with 95% confidence intervals (CI)] relative to the control condition.

Results: Glucose iAUC during the SRA condition was not significantly different from the prolonged sitting condition [EC=0.92 (CI 0.73-1.16), *P*=0.43]. However, SRAs lowered the postprandial insulin response by 26% [EC=0.74 (CI 0.64-0.85), *P*<0.001], and a 23% lowering of the iAUC for insulin:glucose [EC=0.77 (CI, 0.67-0.89), *P*<0.001].

Conclusion: In adults with overweight/obesity, frequent interruptions to sitting time with SRAs lowered postprandial insulin responses and insulin:glucose. These findings may have implications for mitigating cardiometabolic risk in adults with overweight/obesity, who engage in prolonged periods of sitting.

INTRODUCTION

The prevalence of obesity is increasing worldwide, along with concurrent trends in obesity-related conditions including insulin resistance, type 2 diabetes and cardiovascular disease(1) Regular physical activity remains a cornerstone strategy to treat and prevent these conditions. Even in the absence of weight loss, increased moderate-to-vigorous physical activity (MVPA) is associated with improvement in comorbidities, including insulin resistance, impaired glucose tolerance and hypertension.(2) However, less and one-quarter of adults with obesity have been found to achieve the physical activity recommendation of 150min/week of MVPA.(3, 4, 5) Poor participation rates may relate, in part, to the physical consequences of obesity – including mobility issues, musculoskeletal discomfort, tiredness and exertion-related dyspnea and heat intolerance.(6)

Although the relationship between sedentary behavior (put simply, too much sitting as distinct from too little physical activity) and obesity is complex, adults with obesity spend a higher proportion of time sedentary than those without obesity.(5, 7) Observational studies indicate that higher volumes of daily sitting time are independently associated with increased risk of type 2 diabetes, cardiovascular disease and all-cause mortality, even among those who meet physical activity recommendations.(8, 9) Furthermore, prolonged uninterrupted sitting can be associated with a less favorable cardiometabolic profile than an equivalent amount of sitting accumulated in shorter bouts.(10, 11) Frequent breaks in sitting (transitions from sitting to standing/movement) are associated with lower waist circumference, body mass index (BMI), serum triglycerides and 2-hour glucose.(10)

Building on this observational evidence, findings from recent acute experimental trials also suggest that regularly breaking up prolonged sitting time with brief bouts of light- or moderate-intensity walking can lower postprandial glucose and insulin responses in those who are overweight/obese.(12, 13) Although promising, potential barriers exist for implementation of such interventions in workplace settings due to confined space, inability to leave desk/workstation and costs associated with refitting/installation of active workstations. In such contexts, pragmatic approaches to breaking up prolonged sitting may be required.

We recently demonstrated that brief, 3-min bouts of bodyweight resistance activities [simple resistance activities (SRAs): half-squats, calf raises, gluteal contractions and knee raises] were as, if not more, effective than equivalent durations of walking breaks for improving

cardiometabolic outcomes in those with type 2 diabetes.(14, 15) These SRA's target the large muscle groups of the lower body and, most notably, do not require people to move away from their desks at work – factors which may present barriers to workplace productivity and longer-term adherence.

The potential of brief, simple resistance activities to improve metabolic outcomes in populations without type 2 diabetes is yet to be investigated. Thus, we examined the effect of prolonged sitting with and without frequent brief bouts of SRAs on postprandial glucose and insulin levels in adults who were overweight/obese.

METHODS

Study Overview

Physically inactive, sedentary and injury-free adults with overweight/obesity were recruited for a randomized crossover study conducted at Baker Heart and Diabetes institute (Melbourne Australia) between March 2016 and July 2017. Condition order was randomly assigned by a third party using computer-generated random numbers (block randomization and random block sizes), stratified by sex. Study participants were randomized after obtaining informed consent and once eligibility was confirmed.

As previously described,(16) this study involved two acute experimental conditions (each of 6 hours duration), separated by a minimum 6-day washout period. The experimental conditions were prolonged uninterrupted sitting (SIT) and sitting that was regularly interrupted with SRAs. We used a 6-day washout period, as we have previously demonstrated that 3 consecutive days of prolonged sitting or interrupted sitting had no cumulative effect on postprandial glucose and insulin responses.(13) In light of these findings, we felt that there is unlikely to be carryover between treatments with a washout period of this duration.

The primary outcome of the study was endothelial function, as previously reported,(16) with postprandial glucose and insulin responses (determined as incremental area-under-the-curve) being predefined secondary outcomes. It was determined that 19 completions would be required to see the anticipated effect size in the primary outcome. Since postprandial glucose and insulin responses provide key, complementary information alongside the nominated primary endpoint, the current trial was also powered for secondary outcomes. Based on previous findings,(12, 13) it was calculated that 19 completions would detect anticipated

between-condition differences (SIT vs SRA) in postprandial glucose (effect size = 0.70) with 81% power and the co-secondary endpoint (postprandial insulin, effect size = 0.70) with 82% power.

Study participants

Eligibility was based on age (35-75 years), BMI between 25-40kg/m^2 and English-speaking. Exclusions included pregnancy, employment in a non-sedentary occupation (where self-reported sitting time < 50% of total work time), regular participation in moderate-intensity exercise (≥150min per week) for more than 3 months, diagnosed diabetes, use of glucose or lipid-lowering medications, smoking, known physical activity contraindications, or major illness/physical problems (acute or chronic). Pre-menopausal women were excluded (determined from self-report). One woman who reported being peri-menopausal completed both study conditions. Sensitivity analysis (data not shown) revealed that statistical significance and interpretation of the study findings was unchanged by removal of this participant's data.

Characteristics of participants are shown in the Table below. Written informed consent was obtained from all participants following an explanation of study procedures. This study was conducted in accordance with the principles of the Declaration of Helsinki (2008) and approval was obtained by the Alfred Hospital Human Ethics Committee.

Protocol

Participants were asked to refrain from exercise, caffeine, and alcohol for 48 hours prior to each experimental condition. In the week preceding the first experimental condition, participants wore an Actigraph GTX3+ accelerometer around the hip during waking hours. Accelerometer data (60sec epochs) was categorized as moderate-to-vigorous intensity (≥1,952 counts/min) and light-intensity (100-1,951 counts/min) on valid days (defined as having ≥ 10 hours of recorded activity). (17) Daily wear time was derived from a combination of self-report and an automated estimation.

Dietary intake was strictly controlled and standardized across conditions from the evening meal prior to the completion of experimental visits. A pre-condition food pack, containing a microwaveable meal and snack, was provided for the participants to consume in the evening

(between 7-9pm) before conditions. The same pre-condition evening meal was given to each participant, with the meals providing, on average, 3407 ± 483kJ (mean $\pm$ SD), 31.2 ± 4.4 g of protein, 105 ± 12.6 g of carbohydrate and 28.3 ± 6.2g of fat.

On condition days, breakfast provided 33% of daily energy requirements (Schofield equation, 1.5 physical activity level),[18] with a macronutrient profile of 53-55% energy from carbohydrates, 12-15% energy from protein and 30-33% energy from fat. Participants were given 15-minutes to consume their breakfast, which consisted of a ham and cheese croissant, juice and wheat- or corn-based cereal with milk. All participants consumed the meal within the allotted time frame. Water was consumed *ad libitum* during the first trial condition and the same volume was consumed on the subsequent visit.

On condition days, participants arrived at the research rooms at the Baker Heart and Diabetes Institute between 7:30am and 8:00am. Upon arrival, they underwent checks of preparation for the visit and assessments of anthropometry and blood pressure with participants seated for most of this time. Approximately 25-30mins after arrival, a catheter was inserted in an antecubital vein to allow for hourly blood collection. Participants then commenced a 1-hour steady-state period, during which time they remained seated. Following the steady–state phase and completion of a 12-hour overnight fast, participants ate breakfast at time 0 (see Figure 1) and began one of the following protocols for the next 5 hours:

SIT – Participants sat in a comfortable lounge chair and had access to magazines, newspaper, television and DVDs. They were allowed to visit the toilet when necessary.

SRA – The protocol was the same for SIT, with the exception that participants rose from the seated position every 30 minutes and completed a 3-minute bout of SRA. These included nine 20-second rotations of body weight squats, calf raises and single leg knee raises with a brief gluteal contraction. To ensure consistency of the activities, participants mimicked a video demonstration under the supervision of research staff. After each SRA bout, they rated their perceived exertion using the standard 6-20 Borg scale.[19]

Assessment of metabolic outcomes

Venous plasma was collected at -1, 0, 0.5, 1.0, 2.0, 3.0, 4.0 and 5.0 hours. Plasma glucose was measured using the hexokinase method on an Abbott Architect ci16200 analyzer (Abbott

Diagnostics, Santa Clara, California, USA) by an independent laboratory. Plasma insulin was measured in-house using a radioimmunoassay, as per the manufacturer's instructions (HI-14K, Merck Millipore, Bayswater, Victoria, Australia). To minimize inter-assay variability, samples collected from the same participant for both trial conditions were included in the same insulin assay.

Positive incremental area-under-the-curve (iAUC) was computed using the trapezoidal rule from the timed measurements of glucose and insulin post-breakfast, ignoring the area beneath the fasting concentrations. Fasting concentrations were calculated as the mean of the venous plasma samples collected at -1.0 and 0 hours. Postprandial hyperglycemia was defined as >7.8mmol/l (140mg/dl) after ingestion of breakfast.(20) Surrogate indices of insulin resistance and β-cell dysfunction were calculated with the Homeostasis Model Assessment 2 (HOMA2) calculator released by the Diabetes Trials Unit of the University of Oxford (available at http://www.dtu.ox.ac.uk/homacalculator/index.php, Updated February 2017). In the absence of reference ranges for HOMA2, values were interpreted with respect to our previous studies involving adults with overweight/obesity (12, 13) and type 2 diabetes (14) as the same analytical technique was employed.

Data analysis

This study was analyzed on a complete-case basis.(16) Two randomized participants were excluded post-screening (and prior to the first study condition) due to uncontrolled hypertension (by physician direction) and previously undiagnosed type 2 diabetes (an exclusion criterion). Of the 19 study completers, one did not adhere to the recommendation to refrain from moderate-to-vigorous physical activity (MVPA) in the 48-hour period prior to conditions; although the MVPA time was >3 standard deviations from the cohort average, post-hoc analysis revealed that removal of this participant did not influence study outcomes and, as such, a per-protocol analysis was not warranted.

Mixed effects log-linear regressions were used to evaluate the differences between conditions using Stata statistical analysis software (Version 14, StataCorp LP). As metabolic outcomes (glucose and insulin) were log-normally distributed, analysis was performed on the log-transformed data and all models were adjusted for potential confounders (age, sex, BMI, pre-prandial values and treatment order). Outcomes summary statistics were displayed using the exponentiated regression coefficients to provide an estimate of the relative efficacy of

breaking up sitting to reduce postprandial responses on an interpretable scale (ie. multiplicative change). Subsidiary linear regression analyses were also performed to describe the discrete relationships of metabolic outcomes and indices of insulin resistance, after observing that the relationships differed between conditions (condition x HOMA2-IR interaction term). Spearman rank correlations of log-transformed insulin iAUC versus log-transformed HOMA2-IR were performed, based on the known linear log-log relationship of these two variables.(21) Statistical significance was set at *P*<0.05.

RESULTS

Participant characteristics

This study included 19 men and women who were classified as overweight and obese (see Table 1). Accelerometer data collected during the preceding habitual wear period indicated that sedentary time and time spent in light-intensity physical activity contributed to 95.6% of the monitor wear time, with each contributing 8.4hrs/d and 3.9hrs/d, respectively. Mean MVPA time was 34.7mins/d, with 7 participants exceeding 30mins/d, and 2 exceeding the 60mins/day. Mean MVPA was influenced by one highly active participant who accumulated on average 2.1hrs/d. When this participant was removed from the dataset, mean MVPA time was 29.4 mins/d.

Mean fasting plasma glucose and insulin and the HOMA2 indices are shown in Table 1. Compared to our previous studies involving those who were overweight/obese (see Table S1),(12, 13) this cohort was more insulin resistant (*P*<0.05 for comparisons of HOMA2-IR) and had better β-cell function (*P*<0.01 for comparisons of HOMA2-β).

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Study outcomes

Figure 1(a)-(c) shows timed measurements of plasma glucose and insulin during the two experimental conditions. Postprandial glucose profiles did not differ between conditions, with mean values reflecting a state of normal glucose control. In the mixed effect log-linear regression, glucose iAUC during the SRA condition was not statistically different from the SIT condition (exponentiated coefficient, 0.92; 95% CI, 0.73, 1.16, see Figure 1d). However, postprandial insulin concentrations were attenuated during the SRA condition compared with SIT (Figure 1b). This was evidenced by a 26% lower insulin iAUC in SRA (exponentiated

coefficient, 0.74; 95% CI, 0.64, 0.85) compared with SIT. The insulin:glucose ratio, which reflects the variation in insulin response to postprandial glycemia (Figure 1c), was 23% lower for SRA (exponentiated coefficient, 0.77; 95% CI, 0.67, 0.89) compared with SIT.

The relationship of HOMA2-IR and insulin iAUC differed between conditions, as the condition x HOMA2-IR interaction term was significant (P=0.014). In the SIT condition, the log of HOMA2-IR explained 45% of the variance in the log of insulin iAUC (r=0.66, P=0.002), whereas in the SRA condition it only explained 24% (r=0.49, P=0.03).

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DISCUSSION

Our findings provide initial proof-of-concept evidence to inform future trials examining the potential benefits of reductions in sitting in those who are overweight/obese. While glucose concentrations were maintained within normal limits and were not different between conditions, frequently interrupting sitting with brief bouts of SRAs attenuated postprandial hyperinsulinemia, as demonstrated by a 26% lower incremental insulin response. The observation that normoglycemia was maintained, despite significantly lower insulin concentrations for SRAs, suggests that SRAs may have an insulin 'sparing' effect in adults with overweight/obesity.

Contrary to our hypothesis, postprandial glucose responses did not differ between conditions. Previous studies in similar populations have demonstrated that interrupting sitting with walking breaks lowers both glucose and insulin responses.(12, 13, 14, 22) Although some studies have observed no effects of interruptions to sitting, these have generally been observed in healthy/normal weight(23, 24, 25) and/or younger(26) participants, or when the energy expenditure related to the type of break was low.(26, 27) We have previously shown that interrupting sitting with light-intensity walking or SRAs had similar effects on glucose and insulin in those with type 2 diabetes.(14) Since the energy expenditure of the SRAs was marginally higher than that of light-intensity walking (1.5 vs 1.9 METS),(14) we anticipated that the SRA condition would have produced similar metabolic benefits to those previously seen with light-walking breaks in populations with obesity. However, as this study did not include a walking break condition for comparison, we are not able to discern whether the lack of a glucose-lowering effect was related to the type or intensity of the activity adopted during

interruptions from sitting. Other factors, including the meal type and composition (ie. carbohydrate amount and glycemic load), the habitual level of objectively measured MVPA and the metabolic phenotypes of the different cohorts, are also likely to contribute to the variability between studies in glucose outcomes.

Compared to previous studies of interrupting sitting time involving those with overweight/obesity (12, 13) or type 2 diabetes,(20) our study participants demonstrated greater β-cell function (HOMA2-%β) and were more insulin resistant (HOMA2-IR). As participants maintained normal glucose control in both the SIT and SRA conditions, it is possible that the greater β-cell function was able to compensate for the underlying degree of insulin resistance and absence of skeletal muscle contractions during prolonged sitting, through a proportionate rise in insulin response. Although mechanistic determinants were not assessed, we anticipate that the SRAs would promote contractile-mediated glucose uptake,(28) as well as hemodynamic changes (e.g., tissue perfusion, blood volume increment and capillary permeability) associated with the muscular activity.(29) These effects may occur in an additive manner to insulin-mediated glucose uptake, as suggested by the lower insulin to glucose ratio. In contrast, a higher insulin response for the same level of glucose control in the SIT condition, suggests that hypersecretion of insulin was necessary to compensate for a state of sitting-induced insulin resistance. When we examined the relationships of insulin with HOMA2-IR in each of the conditions, we found that HOMA2-IR explained more of the variance in insulin response in SIT than for SRA. Given the discrete relationships of insulin and HOMA-IR in the SIT and SRA conditions, it is reasonable to suggest that frequent intermittent bouts of SRA during sitting 'spared' the compensatory hyperinsulinemia associated with insulin resistance in this sample of individuals with overweight/obesity.

The finding that SRAs lowered postprandial insulin, without corresponding changes in postprandial glucose, may have implications for cardiometabolic risk in those with overweight/obesity. Even in those with normal glucose tolerance, hyperinsulinemia predicts the future risk of developing type 2 diabetes and cardiovascular disease.(30, 31, 32) Hyperinsulinemia and its associated insulin resistance are often considered to be the link between obesity and a clustering of cardiometabolic risk factors (dyslipidemia, hypertension, glucose intolerance).(33) Although these risk factors are highly correlated, hyperinsulinemia has been identified as an independent risk factor in the development of obesity, type 2

diabetes and heart disease.(34, 35, 36) Insulin resistance is often recognized as the first step in the pathophysiology linking obesity to type 2 diabetes,(37) however the transition from normoglycemia to hyperglycemia is characterized by inadequate β-cell compensation for a given degree of insulin resistance.(38) Lifestyle and pharmacologic interventions that reduce the insulin secretory demand on β-cells have been shown to slow or arrest the deterioration of β-cell function that causes diabetes.(39, 40, 41) Although additional evidence is needed, this would suggest that the relative reduction in postprandial insulin seen in our findings points to a putative mechanism through which breaking up sitting with short bouts of activity may help to reduce long-term disease risk.

Our findings add to the growing body of evidence indicating that reducing and breaking up sitting with brief bouts of activity may be an effective approach in mitigating cardiometabolic risk for those with overweight/obesity. Importantly, the SRA breaks can provide an alternative option to walking, which usually obliges someone (e.g. an office worker) to leave his or her immediate workspace. Resistance activities also do not require a large amount of floor space or specialized equipment, and can be done in a variety of settings (workplace or domestic environments). Even though our participants achieved >30 minutes of MVPA at baseline, the 8.4 hours of sedentary time accumulated per day suggests that breaking up sitting could be a supplementary approach to the well-established MVPA guidelines. Our study cohort completed 100% of the SRA bouts and the level of perceived exertion (range 7-11) was comparable to responses seen with gentle walking breaks.(12, 13) As such, SRAs may be an amenable strategy for those who have lower physical function and/or experience discomfort during exercise, and could potentially offer a stepping-stone towards the fulfillment of higher intensity and longer duration physical activity.

This study had several strengths, including the low attrition rate, the strict control of experimental protocols, and the crossover design, which increases internal validity of the study findings. However, the study was not without limitations. Sample size estimates were based on previous studies that differed in relation to indices of insulin sensitivity and β-cell function. We suspect that the inherent natural variation in metabolic phenotypes in the population with overweight/obesity hindered our ability to detect between-treatment differences in postprandial glycemia. However, we cannot rule out that the type of break may also be responsible for the null findings, as this was a point-of-difference from previous work that showed a blood glucose-lowering effect with ambulatory breaks. Other issues include the

high level of objectively measured MVPA of our study sample (even though self-reported levels were <150mins/week), failure to determine insulin secretion (from c-peptide) or the influence of hepatic insulin clearance during experimental protocols, infrequent (hourly only) plasma sampling beyond the 1-hour time point, and the fact that condition-effects were only examined during the post-breakfast period.

In conclusion, regularly interrupting sitting time with brief bouts of simple resistance activities reduced postprandial insulin, but not postprandial glycemia in adults with overweight/obesity. The maintenance of normal post-prandial glucose during experimental protocols may be explained by differences in activity-break mode or greater β-cell function compared to that of previous studies. As such, it would be informative to examine the comparative efficacy of different modes, frequencies and durations of activity used to interrupt periods of prolonged sitting, across different metabolic phenotypes. Longer duration, free-living and feasibility studies will also be required, including further elucidation of potential mechanisms linking changes in these behaviors to cardiometabolic disease.

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**Table 1: Participant characteristics and pre-condition variables**

Participant characteristics	
Male, n (%)	11 (58%)
Age (years)	57 ± 12
Weight (kg)	89.5 ± 11.9
BMI (kg/m^2)	30.6 ± 3.4
Waist circumference (cm)	104.3 ± 10.3
Accelerometer data during habitual period†	
Average wear time (mins/d)	772 ± 47
Sedentary time (mins/d)	503 ± 65
Light-intensity activity time (mins/d)	235 ± 60
Moderate-vigorous intensity activity time (mins/d)	35 ± 31

MVPA ≥30 and <60 mins/d, n (%)	7 (37%)
MVPA ≥60mins/d, n (%)	2 (11%)
Condition days‡	
Fasting glucose (mmol/L)	5.0 ± 0.8
Fasting insulin (pmol/L)	97.7 ± 43.1
HOMA2-IR	1.8 ± 0.8
HOMA2-% β	143.2 ± 44.7

Data are presented as number (%) or mean (± SD) of data for both conditions. †Habitual period excludes the 48 hour 'restrictive' period before each experimental condition. ‡Data refers to the average of samples taken at time 0 on SIT and SRA conditions.

No statistically significant differences were observed between-conditions in any of the pre-condition variables.

Figure 1(a)-(c). Unadjusted postprandial glucose, insulin and insulin:glucose (mean ± SD) profiles during steady-state and physical activity protocols. Closed marker + unbroken line = SIT; open marker + broken line = SRA. (d) Relative efficacy of breaking up sitting to reduce postprandial responses (multiplicative change). Dotted horizontal lines in 1(a) represent reference for postmeal normoglycemia(20)
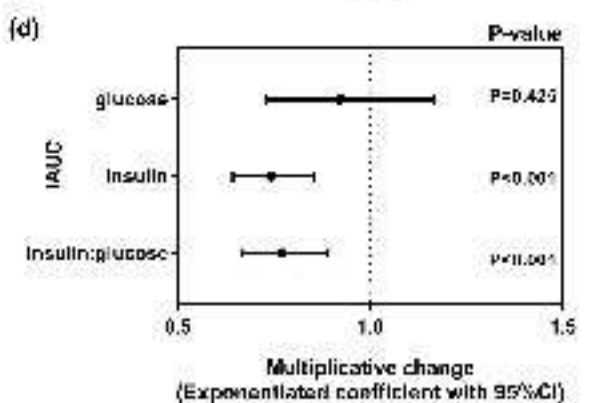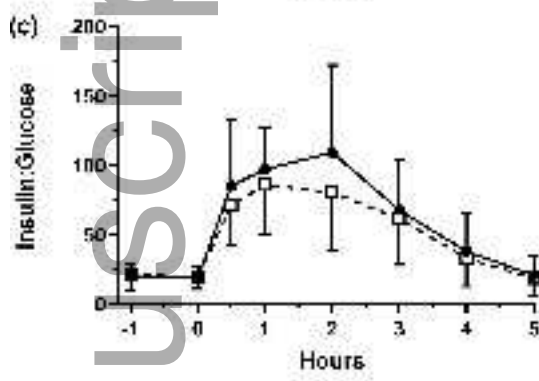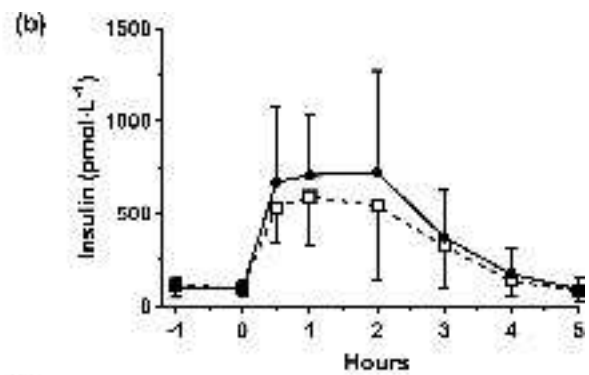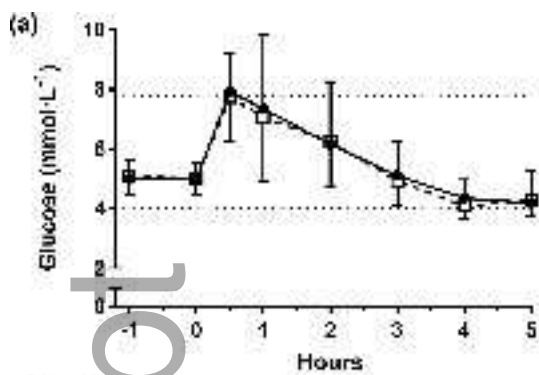
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