The GALAXY-2 project: Galactose – a glucose-stabilizing fuel for skeletal muscle during exercise in individuals with type 1 diabetes

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STUDY SITES

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Background

Exercise is a crucial component of diabetes management in Type 1 Diabetes (T1D), as it helps improve health, glycemic control, and body composition (1). However, a big challenge for these individuals is to maintain stable glucose levels and to avoid hyper- and hypoglycemia during and after exercise. To avoid hypoglycemia, it is often necessary to consume carbohydrates before, during, and after exercise (2). However, the high glycemic response from many carbohydrate sources consumed before exercise can lead to hyperglycemia, followed by a rapid decline in glucose levels during exercise which may lead to hypoglycemia (3, 4). A potential approach to addressing both hypo- and hyperglycemia during and after exercise involves the use of alternative carbohydrates such as fructose and galactose (5). Fructose and galactose primarily undergoes conversion to glucose in the liver, resulting in a prolonged steady release of glucose into the bloodstream, leading to significantly lower glucose fluctuations compared to glucose intake, which can lower the risk of hypoglycemia during exercise (6). However, the metabolism of fructose poses a risk of non-alcoholic fatty liver disease due to the stimulation of de novo lipogenesis and inhibition of β-fatty acid oxidation (7). Galactose, another important dietary monosaccharide in a typical Western diet, could be a viable alternative without the adverse hepatic effects. This delayed metabolism could help prevent hyperglycemia before exercise while offering prolonged protection against hypoglycemia during and after exercise through a sustained and moderated glycemic response. An intriguing finding from clinical studies is that when galactose is ingested along with glucose, the increase in plasma galactose is attenuated

compared to when galactose is consumed alone (8). Our group has recently observed this same pattern in our ongoing study of individuals with T1D, which suggests that this is an insulinindependent effect (Figure 1). The explanation for this effect is still not understood, but we hypothesize the co-ingestion with glucose will increase the hepatic uptake of galactose. Galactose is metabolized through the Leloir pathway (9), but most of the key enzymes and their encoding genes have primarily been studied in yeast (10) and bacteria (11). Professor Gareth Wallis has conducted research on galactose metabolism during exercise and examined the expression of key enzymes involved in the Leloir pathway in human skeletal muscle tissue (12).

Preliminary studies

To explore the potential of galactose as a carbohydrate source for exercise in T1D, we initiated the GALAXY-1 study, supported by the Novo Nordisk Foundation. Here, we performed a randomized, double-blind, crossover study of 14 individuals with T1D who consumed a drink containing 20 g of dextrose, lactose, galactose, or placebo (non-caloric sweetener) 30 minutes before cycling 60-minutes at 50% W_{max}. This study showed that pre-exercise lactose and galactose provided more stable glycemic responses than dextrose and lowered hypoglycemia risk compared to placebo (Figure 2).
These findings support their potential as effective pre-exercise nutrition strategies for individuals with (T1D). To evaluate the potential of galactose as a substrate for skeletal muscle metabolism, we conducted a randomized crossover study in eight healthy participants. Each participant completed two experimental study days involving continuous galactose infusion, with and without a hyperinsulinemic-euglycemic clamp. A unilateral leg exercise protocol was used, where the right leg performed exercise and the left leg served as a non-exercising control (13). Using positron emission tomography (PET) scan with the radiotracer 2-(^{18}F)fluoro-2-deoxy-D-galactose (FDGal), we demonstrated that galactose is taken up by skeletal muscle and that this uptake is enhanced following exercise and insulin infusion (Figure 3). However, it remains unclear whether orally ingested galactose is taken up and utilized by skeletal muscle and liver after exercise. While our previous findings in individuals with T1D demonstrated that galactose may help stabilize glucose levels during aerobic exercise, it is not yet clear whether galactose can contribute to glycogen resynthesis in skeletal muscle after high-intensity exercise. If galactose supports glycogen restoration after exercise without causing significant fluctuations in blood glucose, this could represent a novel strategy to mitigate post-exercise hypoglycemia for people with T1D.

Aim

Aim: To determine whether exercise can stimulate uptake of ingested galactose into skeletal muscle in healthy individuals and in those with T1D.

Hypothesis

We hypothesize that:

- Exercise enhances the uptake of orally ingested galactose in skeletal muscle in individuals with and without T1D
- Co-ingestion of galactose and glucose attenuates the uptake of galactose in skeletal muscle due to an increase in hepatic galactose clearance.

Endpoints

- Primary endpoint: Skeletal muscle galactose uptake rate (μmol/min/g) measured with FDGal PET
- Secondary endpoints: Cardiac galactose uptake, cerebral galactose uptake, hepatic galactose uptake, plasma galactose, glucose and insulin levels

Methods

Design

Eight age- and BMI-matched healthy participants and eight individuals with T1D will be studied twice in randomized crossover study with either ingestion of 30 g galactose (study day 1) or 30 g of galactose + 30 g glucose (study day 2) (Figure 4). On each study day, the volunteers will perform a 30-minute one-legged exercise, starting with a 5-minute warm-up, followed by 1-minute intervals at maximum workload, with 2 minutes of rest between intervals. After the exercise bout, the participant will ingest either 1) galactose or 2) galactose + glucose and in both cases 100 MBq FDGal suspended in water. Immediately after ingestion, a low dose CT scan for attenuation correction will be performed followed by a 90-minute dynamic whole-body FDGal PET scan to measure whole-body organspecific galactose uptake. Ten minutes after completion of the dynamic scan, a static FDGal PET scan of the brain will be performed.

Volunteers

Inclusion criteria

a) Age 20-70 years
b) Healthy or T1D
c) BMI 18.5-30 kg/m^2
d) Signed informed consent form

Exclusion criteria

a) Clinically significant heart, lung, kidney, kidney, liver or malignant disease based on information obtained during an initial screening visit as well as blood samples
b) Diabetic nephropathy, neuropathy, and proliferative retinopathy
c) Hypoglycemia unawareness
d) Blood donation within the last 3 months
e) Smoking
f) Alcohol- or substance abuse
g) Participation in other clinical trials involving ionizing radiation within the last 6 months h) Claustrophobia

i) Not being physically able to exercise one leg for one hour

Withdrawal criteria

Volunteers can withdraw from the study at any time should they wish to do so. The project coordinator can also withdraw a patient from the study due to safety concerns. Following withdrawal, a new project participant will be enrolled to replace the withdrawn volunteer.

Volunteer recruitment

We will advertise on Facebook on the site/groups "Aarhus Universitetshopital and Forsøgsperson – Aarhus Universitet", on the online recruiting platform TrialTree, and through direct outreach to sport clubs in cycling, running and triathlon in Jutland, Denmark. This will include notices on club websites, newsletters as well as direct contact with club coordinators who will distribute study information to their members.Patients with T1D will be recruited through the outpatient diabetes clinic at Aarhus University Hospital. Eligible patients may be approached in connection with a scheduled clinical visit, or via a letter of invitation sent through the clinic. For further information please see "informed consent".

Measurements

SCREENING VISIT

Prior to initiation of the study, the participants will be invited to a screening visit and will be informed that they have the right to have a companion accompany them to the screening. At the screening visit, potential volunteers will receive both verbal and written information about the study from the

examining doctor. Full written participant information will be provided at this visit. The reflection period of a minimum of 24 hours begins only after the participant has received both full verbal and written information. Participation is voluntary, and no informed consent will be obtained until the reflection period has elapsed. The information will be provided in a quiet, undisturbed environment at Medical/Steno Aarhus Research Laboratory, Aarhus University Hospital, to ensure that participants can ask questions freely. If a participant meets the inclusion- and exclusion criteria at this point, the participant will be offered to participate in the project. Upon agreement, a written informed consent for participation in the experiment will be obtained. After written informed consent is obtained, a medical history will be recorded, screening blood samples will be collected, and a physical examination will be performed. The blood samples from the screening visit will be destroyed after analysis. We will register the following data and blood samples:

a) Medical history
b) Weight, height, BMI
c) Standard medical examination including pulse and blood pressure
d) blood samples: haemoglobin, HbA1c, glucose, cholesterol, triglyceride, TSH, creatinine, albumin, natrium, potassium, ALAT, ASAT, bilirubin and coagulation parameters.

The information from the participants' medical history will be reviewed to ensure that all inclusion and exclusion criteria are met. After physical examination and blood samples have been approved, patients will be scheduled to attend the Department of Nuclear Medicine and PET Center, Aarhus University Hospital, where the two study days will take place. Participants will be randomized using a computer-generated block randomization scheme to receive galactose or galactose + glucose in a randomized order.

Prior to study days

For 72 hours leading up to the study day, subjects will be asked to avoid alcohol and strenuous physical activity, and they will be asked to fast from 22.00 in the evening before the day of the scan. They will be instructed to consume a weight maintaining diet according to recommended guidelines (approx. 20 % fat, 30 % protein, d and 50 % carbohydrate). The participants are asked to keep a food diary and to match their food intake as accurate as possible before both study days. For participants with T1D, regular basal insulin for pen users and basal rate for insulin pump users are continued, while correction of hyperglycemia with bolus insulin is allowed until 4 hours prior to testing. If the participant present with hypoglycemia (glucose measurement below 3.9 mmol/L) on the study day, prior to testing, 4 tablets of dextrose (12 g) should be consumed. If hypoglycemia still persists after

15 minutes, this procedure should be repeated until euglycemia. If a participant experience severe hypoglycemia (glucose measurement below 2.8 mmol/L) within 24 h hours before testing, a new study day will be arranged. This to avoid that upstream hypoglycemia will affect the glucoregulatory responses during testing, and because of the increased risk of a new hypoglycemic event. If blood glucose 40 minutes prior to initiation of the one-legged exercise, is above 15 mmol/l, a new study day will also be arranged.

1st STUDY DAY:

The volunteers will arrive fasted (12 hours) at the Department of Nuclear Medicine & PET Center at 7.30 a.m. Two venous catheters will be placed in a vein of the lower arm will be placed for administration of intravenous fluids (and glucose if needed) and venous blood sampling. At 08.30 a.m., the participant will initiate a 30-minute one-legged exercise. At 09.30 a.m., they will ingest a 200 ml beverage containing either 30 g of galactose or 30 g galactose + 30 g glucose and 100 MBq FDGal. Immediately after ingestion, a low dose CT scan for attenuation correction will be performed followed by a 90-minute dynamic whole-body FDGal PET scan to measure whole-body organspecific galactose uptake. Ten minutes after completion of the dynamic scan, a static FDGal PET scan of the brain will be performed. During the study day, arterialized vein samples will be drawn to measure galactose, glucose, lactate, fatty acids, and insulin. Moreover, plasma blood glucose measurement will be controlled every 10-15 minutes until the end of the study day. The whole study day will last approximately 6 hours. If a participant develops hypoglycemia (plasma glucose < 3.9 mmol/L) during testing on a study day, a glucose infusion (20%) will be administered to restore and maintain plasma glucose at approximately 5.0 mmol/L. Once euglycemia is achieved and stabilized, the study procedures will continue as planned.

2nd STUDY DAY

The 2nd study day will be identical to the 1st study day and will take place after at least a 7-day washout period. If volunteers ingested galactose during the 1st study day, they would ingest galactose + glucose during the 2nd study day and vice versa.

Statistical considerations

Results will be presented as means ± SD or median with interquartile range. We will use standard statistical methodology to compare results between study days. P-values < 0.05 will be considered statistically significant. Statistical analyses will be carried out using STATA, R, and Graphad Prism.

Sampling size and power calculation

The study is exploratory and proof-of-concept study designed to investigate galactose uptake in skeletal muscle after oral ingestion. Due to the lack of available data, a sample size calculation cannot be performed. Consequently, we have pragmatically selected a sample size of 8, which we anticipate will be adequate if galactose is taken up to a clinically significant degree.

Ethical considerations

Informed consent

Potential volunteers will have access to study information through the above-mentioned recruitment sites, including contact details for the main investigator. Individuals who contact to the main investigator will be asked whether they wish to be contacted by telephone regarding potential participation. A few days later, potential volunteers will be contacted by the main investigator to confirm their interest, and they will receive verbal and written information about the study. Potential volunteers will be given at least 2-3 days to consider participation, and they are informed that it is important that they read the written information about the study. Should a potential volunteer still wish to participate, they will be invited to a screening visit at Aarhus University Hospital. Potential volunteers will be given spoken information about the project, and they can bring a next of kin to the meeting, should they wish to do so. It will be emphasized that participation is voluntary and that the patient can withdraw from the study at any time. Should the volunteer wish to participate in the study at this point, they will be asked to sign an informed consent form. The volunteers will be informed that the informed consent will give us and The Central Denmark Region Committees on Health Research Ethics access to their medical record for the purpose of accessing information about the participant's health status, which is necessary to carry out the research project as well as for monitoring purposes. No information from their medical record will be reviewed before informed consent is obtained. No study-specific examinations will be performed before informed consent is obtained. Volunteers can complain through the patient complaints board. At the end of the trial and after the collection of relevant data, it will be possible for all participants to have a conversation with the principal investigator at the Nuclear Medicine Department and PET Center for an overview of the overall results available regarding the specific participant.

Hazards, side effects and disadvantages

Placement of venous catheters

A total of two venous catheters will be placed in each participant on each study day, one in each lower arm. Placement of venous catheters may be associated with minor discomfort, bruising, or

hematoma formation, and very rarely infection. For participants with T1D, hypoglycemia (blood glucose < 3.9 mmol/l) may occur during the study day, however, glucose levels will be closely monitored and promptly corrected with intravenous glucose infusion, thereby minimizing discomfort and preventing severe hypoglycemia.

Blood sampling

A total of 300 mL of blood will be sampled per study day, separated by a washout period of minimum 7 days, totalling 600 mL across the study. A standard blood donation in Denmark is 400-450 mL in a single session. The 7-day interval between study days allows partial recovery of plasma volume and red blood cell mass. Also, normal haemoglobin at screening is required to be included in the study. The repeated sampling at this interval is therefore not expected to cause clinically significant hematological compromise or pose a risk in any participant group. We will inform volunteers to contact a doctor should they experience signs of infection (redness, swelling, heat, pain) or symptoms of significant blood loss, including dizziness, fatigue, palpitations, or chest discomfort.

Radiation exposure

The overall radiation exposure from participation in the study:

- ^{18}F-FDGal: 100 MBq x 0.038 mSv/MBq = <u>3.8 mSv</u> per oral ingestion
- 2 x low doses CT scan = 0.5 mSv per scan = <u>1 mSv</u> per day

Overall radiation exposure PET/CT: 4.8 mSv per study day = <u>9.6 mSv</u> for the whole study. A radiation exposure of 9.6 mSv corresponds to approximately 3 times the annual background radiation in Denmark. For an average Dane the risk of harm can be noted as the risk of dying of cancer within a lifetime, which in Denmark is 25%. For every Sv the risk of inducing a terminal cancer increases with 5% compared to the general population in Denmark. A dose of 9.6 mSv = 0.0096 Sv increases the risk of inducing a terminal cancer with 0.0096 Sv x 5% = 0.048 %. For the average Dane that is an increased risk of dying from cancer within a lifetime from 25% to 25.048%.

The laboratory has extensive experience with all the mentioned techniques and procedures, and the participant will be under the observation of a doctor and several medical laboratory technologists throughout the study day. Any problems that could occur in connection with the above-mentioned techniques will be handled and treated in the experimental laboratory with the possibility of anesthesia assistance. Should medical problems arise after the study day, the physician responsible for the trial

will provide appropriate follow-up. Outside regular working hours (16:00-08:00), participants are advised to seek medical care through the usual healthcare services.

Termination of the study

If a volunteer should develop serious complications or the investigator suspects that the participant will be in risk of serious events or complication if the volunteer continues as part of the study, the investigator will interrupt the study. The volunteer will receive treatment for complications corresponding to standard clinical practice. This also applies if the participant becomes seriously ill for other reasons. The volunteer can choose to stop the intervention at any time and if they choose to leave the study, no follow-up is required if they do not want it. If the volunteer is withdrawn from the study due to complications, relevant clinical examinations will be carried out and study-related data will be collected in accordance with the trial protocol, provided that the participant is able to complete the examination. If a volunteer leaves the study, a new volunteer will be recruited to the study until 8 participants have completed the study.

Patient data policy during and after the study

Research biobank

During the study, the following biological material will be extracted from each subject:

- Blood samples. It is estimated that 20 mL will be taken as screening blood samples and approx. 300 mL on the study days corresponding to a total of approx. 620 mL. The samples from the study days are frozen with liquid nitrogen and stored with total anonymization at Aarhus University Hospital for later analysis. The samples will be used to compare differences in metabolic biomarkers.

If there is biological material left at the end of the experiment, the remaining material will be transferred to a biobank with pseudonymization at Aarhus University Hospital for future research and stored for a maximum of 15 years before destruction. This will be notified separately to the “den interne fortegnelse over forskningsprojekter Region Midtjylland”. Volunteers will be informed that the biobank is for future medical research and that blood samples can be destroyed at all times on request of the volunteer. The blood samples will not be handed to a third part. The data of each participant will be protected according to the law of data protection and future research on the content of the biobank will be registered at “den interne fortegnelse over forskningsprojekter Region Midtjylland”.

Patient data policy

Data will be registered in a separate Case-Report-Form (CRF) in digital form. All data-treatment will be conducted at Aarhus University Hospital. All study data will be available to the local research Ethics Committee (Central Denmark Region), and the handling of all personally identifiable data will be registered to "den interne fortegnelse over forskningsprojekter Region Midtjylland" and both "databeskyttelsesloven og databeskyttelsesforordningen" will be complied with.

Organization of the study

The study will take place at the department of Nuclear Medicine & PET Center, AUH. We have the expertise, experience and necessary facilities ready to conduct the proposed study. The members of the research group master a wide range of methods and have authored several papers on human substrate metabolism.

Project economy

The study is initiated by the investigators, and the study is financed by a 600.000 DKK grant from Danish Diabetes and Endocrine Academy (10250006), a 1.000.000 DKK grant from Arla Foods, and a 3.167.826 DKK grant from the Independent Research Fund Denmark (5283-00175B). The funds for the project are placed in an account at Aarhus University. The main investigator will be employed as a Postdoc at Aarhus University through the entire study period and will be salaried through Aarhus University (1.000.000 DKK). Cost for materials, technicians and study is 400.000 DKK. Healthy participants will receive a compensation of 500 DKK per study day. Participants with T1D are patients enrolled in a clinical trial and will therefore not receive monetary compensation in accordance with the guidelines from the National Committee on Health Research Ethics. All participants will have transport expenses reimbursed. Transport reimbursement will only apply to the cheapest form of transportation and compensation will be disbursed proportional if the study participant drops out of the study according to "Appendiks 1 – Retningslinjer for vederlag eller andre ydelser til frivillige forsøgspersoner". The main investigator (postdoctoral researcher) is also the CEO of Noutron ApS, a company specializing in the development of sports nutrition for healthy endurance athletes. The findings of this study will not impact the energy products offered by Noutron ApS. As galactose is naturally present in widely accessible food sources, there is no marketing potential in the findings of this study, which seeks to investigate the basic understanding of galactose metabolism during exercise and insulin infusions. The project supervisors or the involved departments at AUH do not have any economic conflicts of interest regarding the study.

Publication of results

Thien Vinh Luong and the other involved researchers will work in collaboration to publish the results. Any reference to or other publication of results from the study can therefore only take place after mutual acceptance from the above-mentioned researchers. Results of the study will be published whether these are positive, negative or inconclusive. Authorship on all papers emerging from the project will be credited in accordance with the Vancouver recommendations.

Scientific justification

The study will be carried out in accordance with the Helsinki Declaration (2002) after approval from the regional Scientific Ethics Committee and the Norwegian Data Protection Authority. Galactose is the third quantitatively important dietary monosaccharide in Western diets and is mainly consumed as lactose through dairy. It has been proposed as an alternative carbohydrate source for individuals with impaired glucose regulation since it elicits a lower glycemic and insulinemic response compared with glucose. This may reduce hyperglycemia before exercise and lower the risk of hypoglycemia during and after exercise in T1D. Traditionally, galactose has been viewed as contributing to peripheral metabolism only indirectly, as it was believed to require hepatic conversion to glucose before utilization. However, our preliminary *in vivo* human data challenge this view by demonstrating that skeletal muscle can directly take up galactose and that this uptake is strongly stimulated by both exercise and insulin. These findings suggest a more dynamic role for galactose in peripheral carbohydrate metabolism than previously appreciated. Although glucose promotes a greater synthesis of post-exercise skeletal muscle glycogen compared with other carbohydrate sources, galactose might be advantageous in settings where glycemic stability is prioritized over glycogen resynthesis, such as in individuals with T1D.

Patients will be exposed to two catheters in each lower arm as well as blood samples with minimal risk of acute or persistent discomfort. In addition, the subjects will be exposed to ionizing radiation equivalent to 9.6 mSv (see above under risks). The total radiation dose corresponds to approx. 3 times background radiation in Denmark in one year, and an increased lifetime risk of contracting malignant disease from 25% to 25.048% for an average Dane. The guidelines in Appendix 2 *Guidelines for ionizing radiation in clinical experiments"* outline that the value for the radiation dose in certain categories of experiments can be adjusted based on the age of the subjects. In our project, we are recruiting participants aged 20 years and older. According to the guidelines, the effective radiation dose for a category IIb experiment is 1-10 mSv for adults. The total effective radiation dose in this

study is limited to 9.6 mSv, which lies well within category IIb guidelines. Our project aims to investigate the potential blood glucose stabilizing effects of galactose. Specifically, we will assess whether oral galactose ingestion can support skeletal muscle glycogen restoration after exercise while maintaining stable blood glucose levels. Demonstrating such an effect could represent a novel strategy to mitigate post-exercise hypoglycemia for people struggling with glycemic variability such as those with T1D. Since galactose is already a component of the typical Western diet, this strategy could be readily implemented as a practical and accessible nutritional intervention for exercise. Overall, the investigators are of the opinion that, based on the above, it can be concluded that any risks and side effects are outweighed by the expected benefits of conducting the study, which will clarify and possibly expand the knowledge regarding the role of galactose to achieve better glycemic control.

Patient compensation in case of adverse events

Since the study participants are healthy adults, the study is covered by both the Patient Insurance Policy and Occupational Safety and Health Policy.

Regulatory affairs

Approval from the local ethics committee will be obtained before initiation of the study. Personal data will be treated confidentially and deleted after the completion of the study. All data will be stored in a secure Redcap database at the Aarhus University servers with logging of all access. Biological material taken during the study day will be frozen for later analyses and excess biological material at the end of the experiment will be transferred to a biobank with pseudonymization at Aarhus University Hospital for future research and stored for a maximum of 15 years before destruction.

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Figure 1. Co-ingestion of glucose and galactose blunts the increase in plasma galactose in individuals with type 1 diabetes.

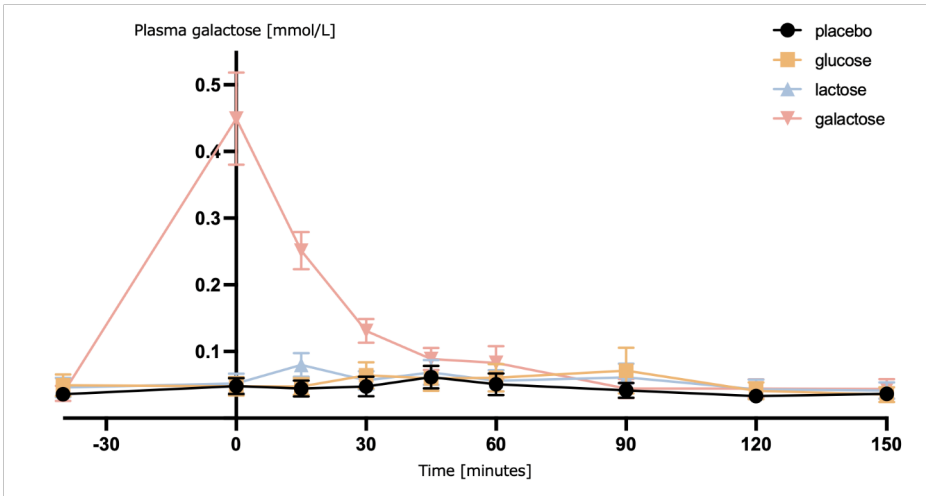


Figure 2. Result from our trial in individuals with type 1 diabetes. Here, we observed less fluctuation in glucose levels during exercise after ingestion of galactose and lactose compared to glucose.

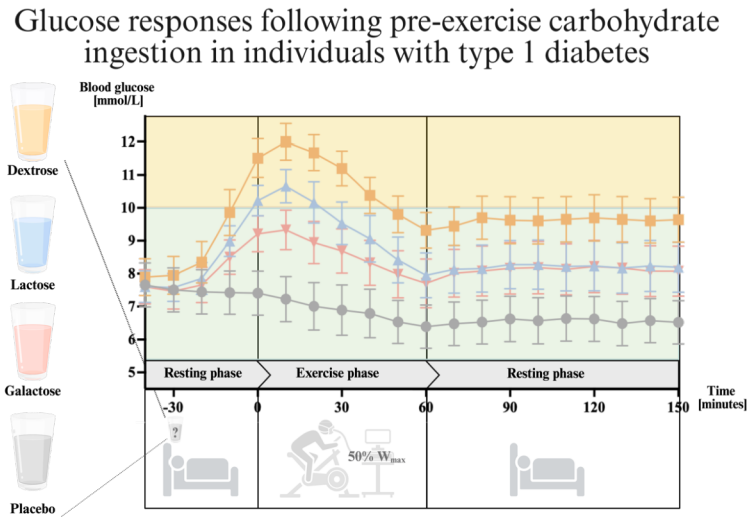


Figure 3. Visual FDGal uptake in the m. quadriceps femoris of both legs during insulin stimulation (A). Comparison of absolute FDGal uptake in m. quadriceps femoris between the exercised right leg and the rested left leg during both with and without insulin stimulation (B), $n = 8$.

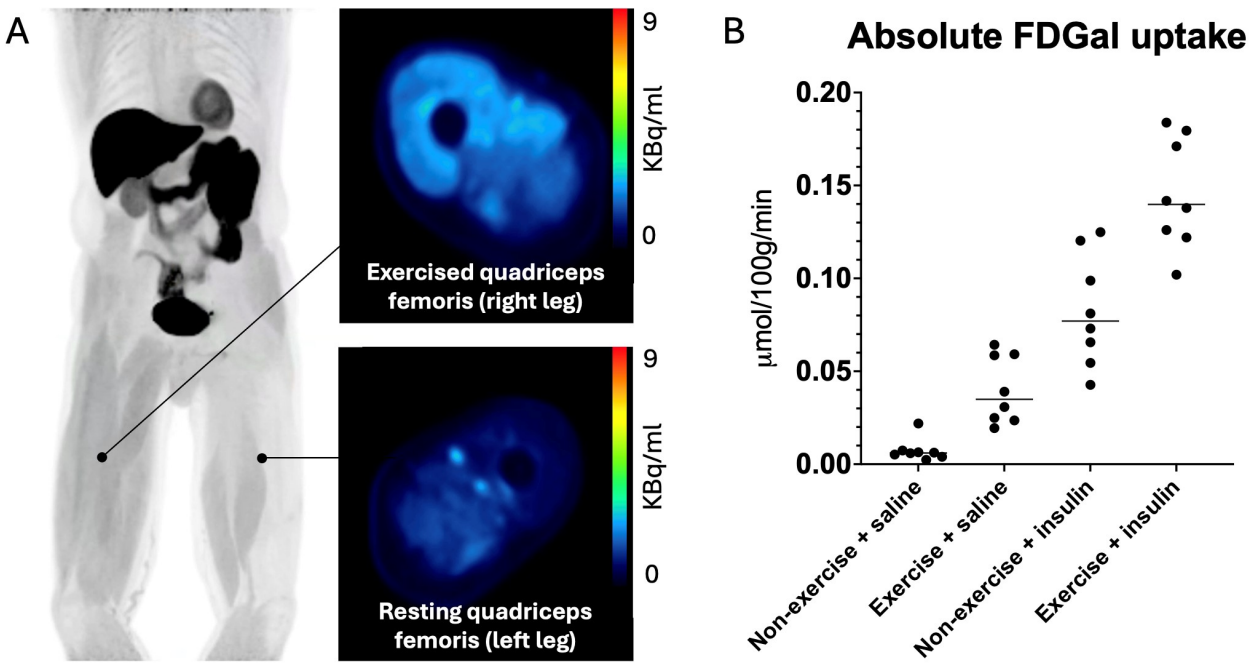


Figure 4. Study day.

