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Exercise and insulin independently stimulate galactose uptake into human skeletal muscle

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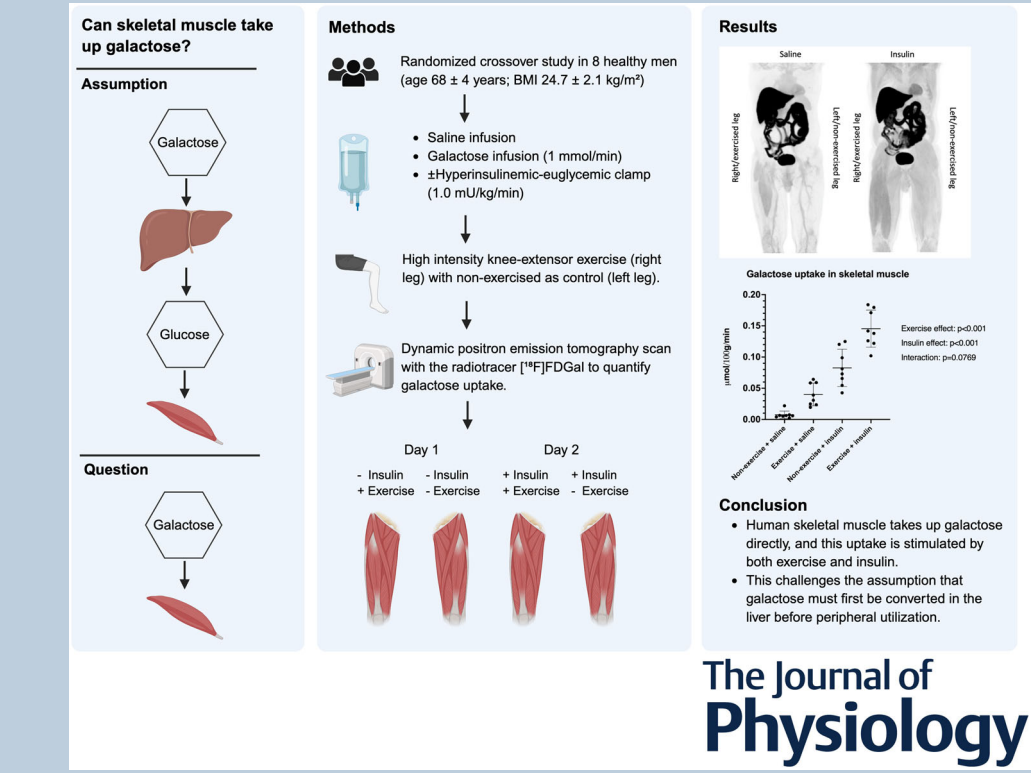

Abstract figure legend Human skeletal muscle can directly take up galactose, and this is independently stimulated by exercise and insulin. Using positron emission tomography (PET) with the galactose analogue [^{18}F]FDGal, combined with one-legged high-intensity knee-extension exercise and a hyperinsulinaemic–euglycaemic clamp, eight healthy older

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men underwent dynamic PET imaging of both thighs. Exercise increased galactose uptake primarily by enhancing muscle blood flow (tracer influx, K1), while insulin increased uptake by promoting intracellular phosphorylation and trapping via galactokinase (k3), with an additive effect when combined. These findings challenge the long-standing assumption that galactose must first be converted to glucose in the liver before peripheral tissues can use it, and instead show that skeletal muscle itself directly metabolises galactose. Because galactose produces smaller blood-glucose excursions than glucose, this may support its use as an exercise carbohydrate for people with impaired glucose regulation, such as those with diabetes.

Abstract Carbohydrate choice affects glycaemic responses during and after exercise, particularly for individuals with impaired glucose regulation. Galactose causes smaller glycaemic excursions than glucose but is thought to require hepatic conversion to glucose via the Leloir pathway before peripheral use. Whether galactose is directly taken up by skeletal muscle, and whether this is regulated by exercise and insulin remains unclear. In this randomised, controlled cross-over trial, eight healthy men (age 68 ± 4 years; body mass index 24.7 ± 2.1 kg/m^2) completed two 4 h study days, with and without a hyperinsulinaemic–euglycaemic clamp (1.0 mU/kg/min). Galactose turnover was assessed using a primed-constant galactose infusion. Participants performed one-legged, high-intensity knee-extension exercise at maximal capacity, with the contralateral leg as a non-exercised control. Skeletal muscle galactose uptake was quantified by dynamic [^{18}F]FDGal positron emission tomography (PET), and arteriovenous (AV) exchange across the leg was determined from femoral blood samples combined with [^{15}O]H_2O PET-measured leg perfusion. Exercise and insulin markedly increased galactose uptake (exercise effect: $P < 0.001$; insulin effect: $P < 0.001$; interaction: $P = 0.0769$). PET analysis showed that exercise primarily increased tracer influx (K1), while insulin increased intracellular trapping (k3) and modestly reduced efflux (k2). Plasma galactose concentrations were low (0.2 ± 0.1 mmol/L) and galactose AV exchange across the leg did not differ across conditions. Human skeletal muscle can directly take up galactose, and this is stimulated by exercise and insulin. This challenges the assumption that hepatic conversion is required before peripheral utilisation. Future studies should determine whether galactose is incorporated into skeletal muscle glycogen to a physiologically relevant extent.

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Key points

- Galactose causes smaller spikes in blood sugar than glucose, and it has long been assumed that the body must first convert galactose into glucose in the liver before peripheral use.
- Using positron emission tomography imaging with the galactose analogue 2-[^{18}F]fluoro-2-deoxygalactose in combination with a one-legged knee-extension ergometer, we demonstrated that human skeletal muscle can directly take up galactose.
- Both exercise and insulin markedly increased skeletal muscle galactose uptake, with an additive effect when combined.
- Exercise primarily increased galactose uptake by enhancing muscle blood flow, whereas insulin exerted its effect by promoting phosphorylation and intracellular trapping.
- Further studies are required to determine whether galactose is incorporated into skeletal muscle glycogen to a physiologically meaningful extent.

Introduction

Carbohydrate choice determines how efficiently a substrate is taken up and utilised by skeletal muscle during and after exercise, as glucose is more readily taken up and incorporated into glycogen than galactose (Podlogar et al., 2023). Despite this, galactose may offer distinct metabolic advantages, as it elicits smaller glycaemic excursions

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than glucose (Jentjens & Jeukendrup, 2003), which may be beneficial for individuals with impaired glucose metabolism, especially those with diabetes (Schmidt et al., 2026). Galactose is commonly consumed in Western diets, primarily as a component of lactose in dairy products (Silanikove et al., 2015). Although total dairy consumption has declined modestly in recent years, consumption *per capita* remains high, averaging approximately 60–130 L of fluid milk and 10–25 kg of solid dairy products annually in populations of Northern European ancestry (Silanikove et al., 2015). Assuming a rough average lactose content of ∼4.6% across dairy products (Portnoy & Barbano, 2021), this corresponds to an estimated annual lactose intake of ∼3.2–7.1 kg per person, equivalent to ∼1.6–3.6 kg of galactose per year or ∼4.4–9.9 g/day. However, despite being one of the three quantitatively important dietary monosaccharides, galactose metabolism remains under-explored. Consequently, fundamental aspects of galactose metabolism in humans remain poorly characterised.

Galactose's lower efficacy for muscle glycogen resynthesis has generally been attributed to the direct uptake of glucose into skeletal muscle, whereas galactose must first undergo hepatic metabolism via the Leloir pathway, where it is converted to uracil-diphosphate (UDP)-glucose and subsequently channelled into glycolysis, hepatic glycogen synthesis, or released into the circulation as glucose for peripheral utilisation (Holden et al., 2003). Consistent with this, ingestion of galactose during exercise leads to an exogenous carbohydrate oxidation rate of only 50%–60% of that observed for glucose (Leijssen et al., 1995), likely reflecting a greater hepatic uptake and incorporation in hepatic glycogen stores (Fried et al., 1996). Interestingly, Leloir pathway enzymes have been identified in skeletal muscle (Podlogar et al., 2023), challenging the prevailing assumption that hepatic conversion of galactose into glucose is necessary before peripheral utilisation. This raises the possibility that skeletal muscle may possess the capacity for direct galactose metabolism. However, the extent to which skeletal muscle can take up galactose *in vivo* remains unknown.

To address this knowledge gap, the present study employed positron emission tomography (PET) with the galactose analogue 2-[^{18}F]fluoro-2-deoxygalactose ([^{18}F]FDGal). This radiolabelled analogue has been developed for clinical imaging of hepatocellular carcinoma due to its high uptake in both normal liver tissue and malignant hepatic cells (Sørensen, Frisch et al., 2011). Following hepatic uptake, the tracer is phosphorylated by galactokinase similarly to native galactose, although its subsequent metabolic fate has not been fully established. However, within the time frame of the PET acquisition, no circulating metabolites have been detected in plasma, rendering tracer retention effectively irreversible and allowing quantification of tissue-specific galactose uptake (Sørensen et al., 2008). Using this method, our aim was to assess skeletal muscle galactose uptake in an exercised and a non-exercised leg under conditions with and without insulin stimulation. For comparison with the PET-derived estimates, we additionally assessed arteriovenous (AV) differences in galactose exchange across the legs. We hypothesised that galactose is directly taken up by skeletal muscle and that this uptake is stimulated by both high-intensity exercise and insulin.

Methods

Ethical approval

The study protocol was approved by the Central Denmark Region Committees on Health Research Ethics (1-10-72-49-23), registered at ClinicalTrials.gov (NCT05986500), and conducted in accordance with the *Declaration of Helsinki*.

Inclusion and participants

All participants attended a screening visit before inclusion, during which demographic data, clinical history, height, weight, blood pressure, pulse and blood samples were collected, and a one-legged high-intensity exercise test was performed. The inclusion criteria were: (1) age 50–75 years and (2) body mass index (BMI) 18.5–30 kg/m^2. The exclusion criteria were: (1) pharmacological treatment that could affect outcome measures such as insulin treatment, antidiabetic medication, statins or beta-blockers; (2) HbA1c >48 mmol/mol; (3) impaired

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cardiac function; (4) impaired renal function (estimated glomerular filtration rate <60 mL/min); (5) liver disease (alanine aminotransferase more than three times the upper limit of 70 U/L); (6) active or previous cancer; (7) anaemia (haemoglobin <6.5 mmol/L); (8) blood donations within the last 3 months; (9) participation in other studies involving radioactive isotopes within the last 6 months; (10) alcohol abuse; and (11) unable to perform the exercise protocol. Informed written consent was obtained from the participants who met the inclusion criteria.

Study days

The study was conducted as a randomised, controlled crossover trial consisting of two study days separated by at least 7 days, differing only in the administration of a hyperinsulinaemic–euglycaemic clamp (HEC) (Fig. 1). The volunteers arrived fasted (12 h) at the Department of Nuclear Medicine at 07.00 h. At 07.30 h catheters were placed, under local anaesthesia using the Seldinger technique, in the femoral vein of both legs with the tip positioned approximately 4 cm proximal to the inguinal ligament. These catheters were used for femoral venous blood sampling. An additional two venous catheters were placed in the cubital veins for administration of intravenous fluids (galactose, saline, glucose and insulin) and venous blood sampling. Lastly, an arterial catheter was placed in the right radial artery for arterial blood sampling. At 09.00 h, a galactose bolus (6 mmol or 1081 mg) was administered, followed by a continuous galactose infusion (1 mmol/min or 180 mg/min) throughout the 240 min study period. This protocol was designed to obtain concentrations of galactose similar to those that can be achieved after galactose ingestion (≈1 mmol/L) (Williams et al., 1983). Simultaneously with the start of the galactose infusion, participants received a 0.9% saline infusion with or without an HEC. During the HEC, insulin (Actrapid, Novo Nordisk, Bagsværd, Denmark) was infused continuously at a rate of 1.0 mU/kg/min and a glucose solution (20%) was infused at variable rates to maintain euglycaemia at 5 mmol/L. At 10.00 h, a low-dose computed tomography (CT) scan for attenuation correction and anatomical localisation was performed followed by a 4 min dynamic PET scan with $[^{15}O]H_2O$ to assess perfusion in both legs. At 10.30 h, participants performed a one-legged exercise protocol, as described below, using the same ergometer as during the screening session. At 11.00 h, a second low-dose CT scan for attenuation correction was performed, followed by another dynamic $[^{15}O]H_2O$ PET scan. Subsequently, skeletal muscle galactose uptake was assessed by intravenous administration of 180 MBq $[^{18}F]$FDGal, followed by a dynamic $[^{18}F]$FDGal PET scan initiated 30 min after exercise.

One-legged exercise

To isolate quadriceps muscle work in the right leg, participants performed high-intensity exercise on a modified Krogh bicycle ergometer (Andersen et al., 1985). During the screening visit, maximal capacity was determined using an incremental exercise protocol performed at a fixed cadence of ≥60 kicks per minute, beginning with a 5 min warm-up at 5 W followed by 1 min at 15 W and a 2 min rest. Workload was then increased by 5 W for each subsequent 1 min exercise bout, each separated by 2 min rest periods, until the required cadence could no longer be maintained. The highest workload at which 60 kicks per minute could be sustained was

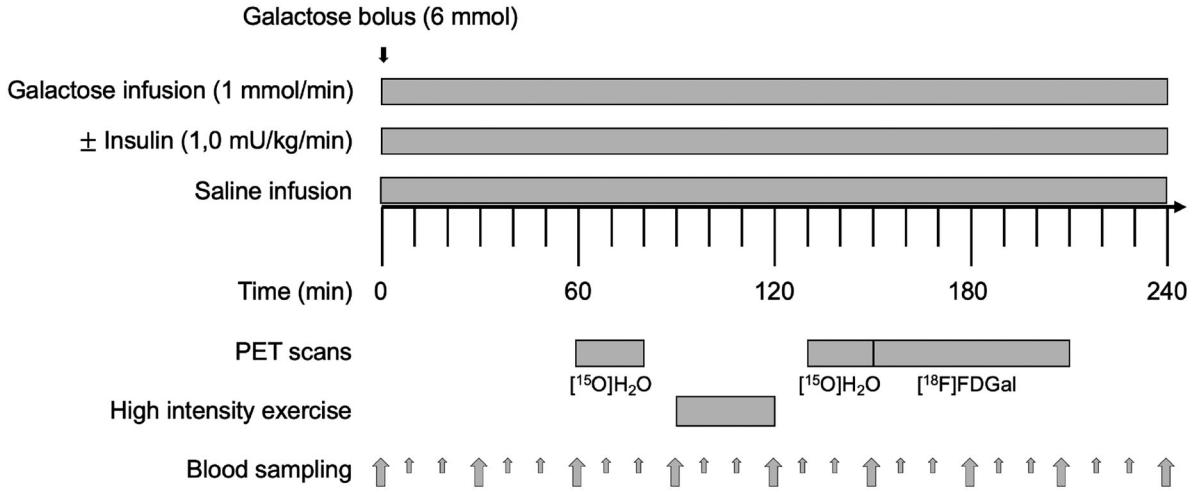

Figure 1.
Study flowchart

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defined as maximal capacity. On study days, participants performed a 5 min warm-up at 5 W followed by seven repetitions of 1 min at maximal capacity, each separated by 2 min rest periods, with the other leg serving as a non-exercise control.

PET scans

Dynamic PET/CT scans were performed using a Biograph Vision Quadra PET/CT system (Siemens, Erlangen, Germany) with a long axial field of view of 106 cm, thereby enabling simultaneous coverage of both thighs and the cardiac blood pool within a single acquisition. The dynamic [^{15}O]H_2O PET scans consisted of 22 frames with the following structure: 1 × 10 s, 8 × 5 s, 4 × 10 s, 2 × 15 s, 3 × 20 s, 2 × 30 s and 2 × 60 s, a total of 6 min. The dynamic [^{18}F]FDGal PET scan consisted of 34 frames with the following temporal structure: 1 × 10 s, 8 × 5 s, 4 × 10 s, 3 × 20 s, 5 × 30 s, 6 × 60 s, 4 × 150 s, 4 × 300 s and 2 × 600 s total of 61 min. For all PET scans, a 106 cm axial field of view was positioned to cover a region from the knees and proximally. The [^{15}O]H_2O images were reconstructed with a voxel size of 2.75 × 2.75 × 3.0 mm and a 5 mm Gaussian post-filter. The [^{18}F]FDGal images were reconstructed with a voxel size of 3.3 × 3.3 × 3.0 mm and a 2 mm Gaussian post-filter.

PET image analysis

Defining organ and tissue volumes of interest on the PET images. All dynamic whole-body PET images were visually inspected using PMOD version 4.4 software (PMOD Technologies Ltd., Zürich, Switzerland). Volumes of interest were manually drawn as large as possible to encompass the four thigh muscles m. vastus lateralis, m. vastus medialis, m. vastus intermedius and m. rectus femoris in both legs. In addition, a volume of interest was drawn in the left ventricular cavity of the heart for the input function. In cases where anatomical placement was challenging, the corresponding CT images were used to assist accurate placement of the volumes of interest. PET time–activity curves were extracted from all volumes of interest and used for subsequent kinetic modelling.

Kinetic analyses. All kinetic analyses were performed using PMOD version 4.4 software. Perfusion at rest and following exercise was assessed using the freely diffusible tracer [^{15}O]H_2O, and data were analysed with a single tissue compartment model. Additionally, it has been validated for assessment of skeletal muscle perfusion in the lower extremities (Christensen et al., 2025). Because the K1 parameter is sensitive to partial volume effects, perfusion was quantified using the k2 parameter. Perfusion across the quadriceps muscles was expressed as a single value by averaging the four individual muscle measurements. Dynamic [^{18}F]FDGal images were analysed using the Patlak model for irreversible processes with the methodology previously described for [^{18}F]FDG (Figs. 2 and 3) (Nielsen et al., 2018). Uptake across the four quadriceps muscles was also calculated as a single value by averaging the four individual muscle measurements. Galactose uptake (μmol/100 g/min) was calculated by multiplying the net influx rate constant Ki (mL/100 g/min) by the plasma galactose concentration (mmol/L) measured immediately prior to the [^{18}F]FDGal PET acquisition at $t = 150$ min. To further characterise the mechanisms underlying galactose uptake, tracer kinetics were also analysed using a two-tissue compartment model in which four rate constants were estimated: K1 (tracer influx from plasma to the free tissue compartment, representing the product of flow and extraction); k2 (efflux from the free tissue compartment back to plasma); k3 (forward transfer from a free to a bound compartment, reflecting galactokinase-mediated phosphorylation and irreversible intracellular trapping of [^{18}F]FDGal-1-phosphate); and k4 (dephosphorylation and back flux from a bound to a free tissue compartment). The rate constant k4 was fixed at zero, consistent with the assumption of irreversible intracellular trapping underlying the Patlak model. Moreover, a lumped constant (LC) of 1 and a vascular fraction of 0 were assumed for skeletal muscle. Although these values may not reflect true physiological constants, they were applied consistently across the two conditions to allow valid comparisons within the crossover study design.

Blood samples

Blood samples for measurement of galactose, glucose, free fatty acids (FFAs), and lactate were collected at nine time points ($t = 0$, 30, 60, 90, 120, 150, 180, 210 and 240 min) during the study days. Additionally, plasma glucose concentration was measured at 10 min intervals during insulin infusion. Galactose concentrations were measured using a colorimetric assay (Thermo Fisher Scientific, Waltham, USA). Glucose and lactate concentrations were analysed using a YSI glucose analyser (YSI Life Sciences, Yellow Springs, OH). Serum FFA concentrations were analysed with an enzymatic colorimetric method assay for non-esterified fatty acids (NEFA)-HR (Wako Chemicals Europe GmbH, Neuss, Germany), and insulin with Insulin Elisa (Mercodia AB, Uppsala, Sweden).

Calculations

For comparison with the PET-derived estimates of galactose uptake, AV differences in substrate exchange rates were calculated based on plasma galactose

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concentrations obtained from simultaneous blood sampling of both femoral veins and the radial artery, combined with leg perfusion measured with $[^{15}O]H_2O$ PET. The AV substrate exchange rates across both legs were quantified using the Fick principle (Visscher & Johnson, 1953). The AV concentration difference was calculated as $\Delta C = C_{arterial} - C_{venous}$, and exchange rate was derived by multiplying ΔC by leg perfusion measured from the $[^{15}O]H_2O$ PET scan. Positive values indicate net tissue uptake while negative values indicate net release. Because K1 reflects the combined contribution of both perfusion and transport capacity, and perfusion increased substantially with exercise, we additionally calculated the permeability–surface area product (PS) to obtain a flow-independent measure of transport capacity. PS was derived from K1 and perfusion (F) using the Renkin-Crone relationship: $PS = -F \cdot \ln(1 - K1/F)$ (Crone, 1963; Renkin, 1959).

Statistics

Statistical analyses and graphs were generated using Stata 14 (College Station, Texas, USA), R version 4.5.2 (R Foundation for Statistical Computing, Vienna, Austria) and GraphPad Prism 10 (San Diego, California, USA). To evaluate normal distribution, QQ plots were examined and the Shapiro-Wilk test was applied to model residuals. Galactose uptake, relative $[^{18}F]$FDGal uptake, the two-tissue compartment model rate constants (K1, k2, k3) and the PS were analysed using linear mixed-effects models with exercise, insulin and their interaction as fixed effects and participant as a random intercept. Residuals for the galactose uptake showed mild heteroscedasticity, but raw units were retained for interpretability, as this did not affect the results. K1, k2 and PS were log-transformed prior to analysis due to right-skewed residuals. A similar model structure was applied to compare muscle perfusion between the exercised and non-exercised leg under saline and insulin conditions before and after exercise. Main effects were reported as 'exercise effect': or 'insulin effect': and the interaction as 'interaction':, followed by the corresponding *P* value. Substrate exchanges were summarised as incremental area under the curve (iAUC) values and analysed using a linear mixed-effects model. This approach was chosen because modelling raw metabolite exchanges resulted in residual heteroskedasticity, and log-transformation was not feasible because of the predominance of negative exchanges. Therefore, iAUC was used as the outcome variable. Treatment condition (non-exercise + saline,

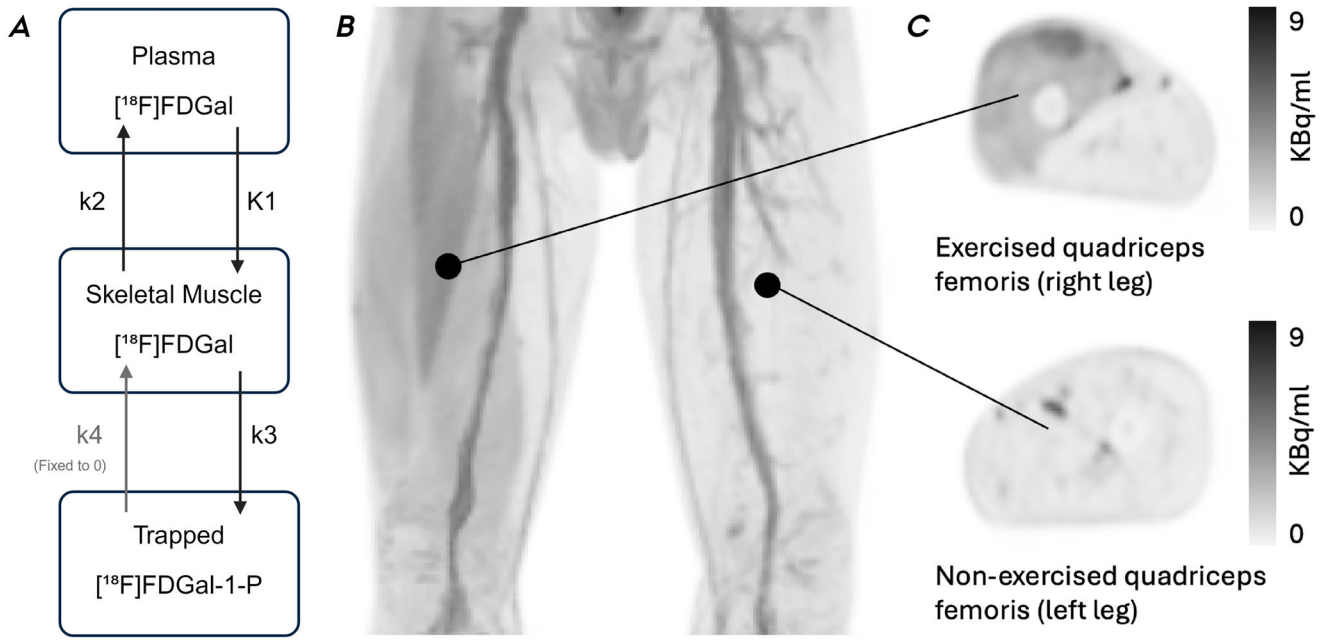

Figure 2. Pharmacokinetic model and PET images of the quadriceps femoris during the saline condition, illustrating exercise-induced alterations in skeletal muscle uptake of $[^{18}F]$FDGal
A, two-tissue compartment model used for kinetic analysis of $[^{18}F]$FDGal, showing plasma, skeletal muscle (free) and trapped ($[^{18}F]$FDGal-1-P) compartments and the corresponding rate constants K1, k2, k3, k4, where k4 was fixed to 0, consistent with irreversible intracellular trapping. *B*, grayscale image showing the anatomical reference of both thighs. *C*, transverse PET images of the exercised quadriceps femoris in the right leg (top) and the non-exercised quadriceps femoris in the left leg (bottom). Uptake of $[^{18}F]$FDGal is visibly higher in the exercised muscle compared with the resting muscle. Abbreviations: $[^{18}F]$FDGal, 2-$[^{18}F]$fluoro-2-deoxygalactose; kBq, kilobecquerel; PET, positron emission tomography.

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exercise + saline, non-exercise + insulin, and exercise + insulin) was included as a fixed effect, and participant as a random intercept. Models were fitted using restricted maximum likelihood with Kenward–Roger degrees of freedom to account for the small sample size. Model assumptions were evaluated using scatterplots and Q–Q plots of residuals. Reported P values represent the overall effect of treatment condition. For iAUC, *post hoc* pairwise comparisons between all four treatment conditions were also performed using estimated marginal means, with unadjusted P values reported. Overall, a P value of <0.05 was considered statistically significant. Data are presented as means ± SD or median with interquartile range, unless stated otherwise. Data in the graphs are displayed as means ± SD or median (interquartile range).

Results

Participants

Eight eligible volunteers were screened. All participants met the inclusion criteria, successfully completed the one-legged exercise test, and were enrolled in the study. Thus, eight participants (8 men; age 68 ± 4 years; BMI 24.7 ± 2.1 kg/m^2) were included in the final cohort. Two participants received antihypertensive treatment while the remaining participants did not receive any medication. One [^{15}O]H_2O PET scan failed for a single participant during one visit, resulting in seven completed perfusion scans during the HEC study days. All other study procedures were completed as planned.

Skeletal muscle galactose uptake and kinetics

Both exercise and insulin markedly increased galactose uptake (non-exercise + saline: 0.01 ± 0.01; exercise + saline: 0.04 ± 0.02; non-exercise + insulin: 0.08 ± 0.03; exercise + insulin: 0.15 ± 0.03 µmol/100 g/min; exercise effect: $P < 0.001$; insulin effect: $P < 0.001$; interaction: $P = 0.0769$) (Fig. 4*A*). The kinetic analysis demonstrated that exercise increased plasma-to-tissue influx of galactose, K1, (non-exercise + saline: 0.03 ± 0.01; exercise + saline: 0.05 ± 0.02; non-exercise + insulin: 0.03 ± 0.01; exercise + insulin: 0.06 ± 0.02 mL/100 g/min; exercise effect: $P < 0.001$; insulin effect: $P = 0.322$; interaction: $P = 0.867$) (Fig. 4*B*).

Insulin reduced efflux of galactose from tissue back to plasma, k2, whereas exercise had no effect (non-exercise + saline: 0.25 ± 0.08; exercise + saline: 0.30 ± 0.08; non-exercise + insulin: 0.21 ± 0.11; exercise + insulin: 0.20 ± 0.10/min; exercise effect: $P = 0.426$; insulin effect: $P = 0.0107$; interaction: $P = 0.198$) (Fig. 4*C*). Insulin markedly increased k3, reflecting increased

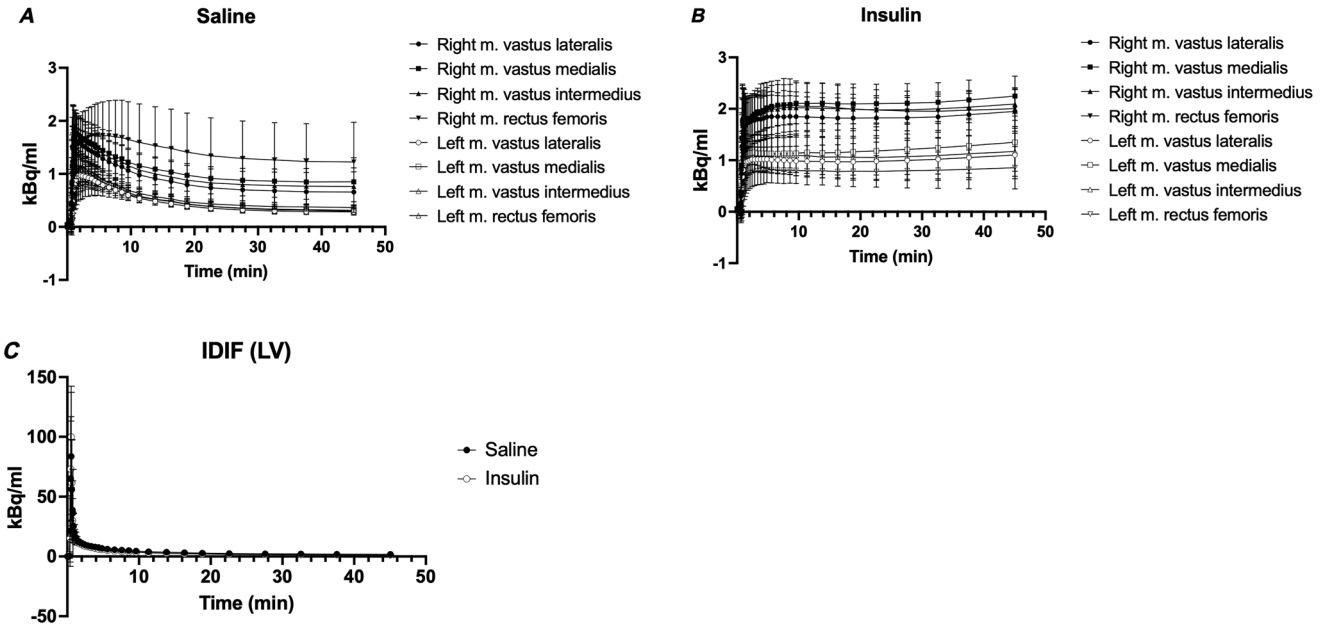

Figure 3. Time–activity curves of [^{18}F]FDGal in the quadriceps femoris and the image-derived input function during the saline and insulin conditions
A, time–activity curves for m. vastus lateralis, m. vastus medialis, m. vastus intermedius and m. rectus femoris in the exercised right leg and the non-exercised left leg during the saline condition. *B*, corresponding time–activity curves during the insulin condition. *C*, image-derived input function obtained from the left ventricular cavity during the saline and insulin conditions. Data are expressed as means with SD, $n = 8$. Abbreviations: [^{18}F]FDGal, 2-[^{18}F]fluoro-2-deoxygalactose; IDIF, image-derived input function; kBq, kilobecquerel; LV, left ventricle.

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galactokinase-mediated phosphorylation and intracellular trapping of galactose (non-exercise + saline: 0.004 ± 0.002; exercise + saline: 0.016 ± 0.008; non-exercise + insulin: 0.051 ± 0.016; exercise + insulin: 0.054 ± 0.019/min; exercise effect: $P = 0.0994$; insulin effect: $P < 0.001$; interaction: $P = 0.375$) (Fig. 4*D*). Exercise increased the PS (non-exercise + saline: 0.03 ± 0.01; exercise + saline: 0.05 ± 0.02; non-exercise + insulin: 0.03 ± 0.02; exercise + insulin: 0.06 ± 0.02 mL/100 g/min; exercise effect: $P < 0.001$; insulin effect: $P = 0.234$; interaction: $P = 0.628$), indicating that the increase in K1 with exercise reflects both elevated perfusion but also an increase in transport capacity.

Substrates and AV differences

Arterial galactose concentrations were low and stable throughout the study day in the saline condition (∼0.1–0.2 mmol/L) with a similar pattern during the insulin condition (Fig. 5*A*). Galactose exchange iAUC did not differ across the four experimental conditions ($P = 0.857$), with values around zero, indicating neither net uptake nor release under any condition (Fig. 6*A*). Arterial glucose concentrations remained largely stable around 5.5–6.5 mmol/L, with a minor increase coinciding with exercise (Fig. 5*B*). During insulin stimulation, arterial glucose concentrations were maintained at approximately 5.0 mmol/L. Glucose exchange iAUC was significantly greater during hyperinsulinaemic

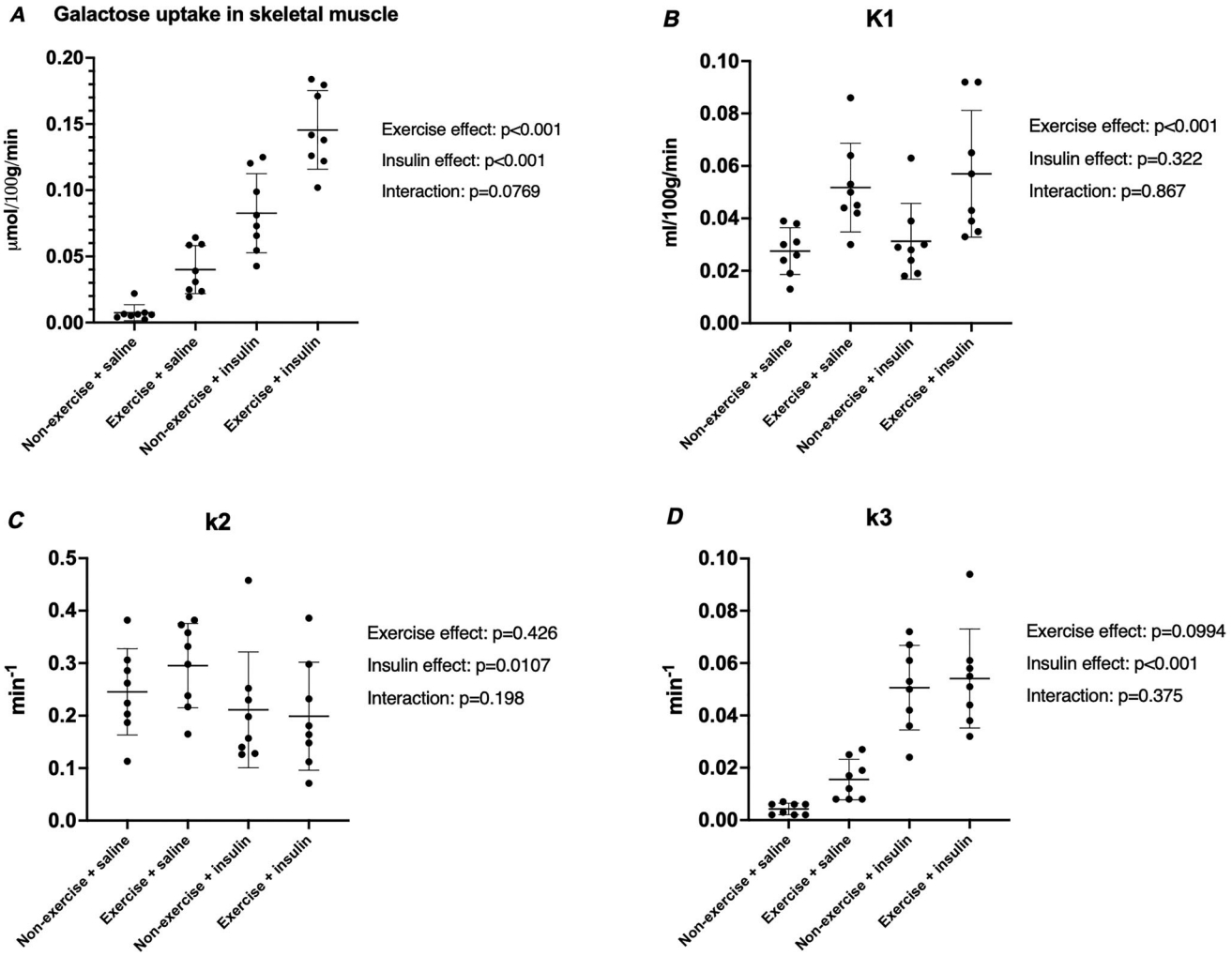

Figure 4. Skeletal muscle galactose uptake and compartmental rate constants in the quadriceps femoris across four treatment conditions: non-exercise + saline, exercise + saline, non-exercise + insulin, and exercise + insulin
A, galactose uptake derived from Patlak PET kinetic modelling. *B*, K1, reflecting tracer influx from plasma to tissue. *C*, k2, reflecting tracer efflux from tissue to plasma. *D*, k3, reflecting intracellular phosphorylation by galactokinase. *B–D* were derived from two-tissue compartment PET kinetic modelling. Data are expressed as means with SD, $n = 8$. Abbreviation: PET, positron emission tomography.

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conditions compared with both saline conditions, reflecting insulin-stimulated net glucose uptake ($P < 0.001$) (Fig. 6*B*). During saline conditions, arterial FFA concentrations started at ∼0.5 mmol/L, declined to ∼0.3 mmol/L, and remained suppressed during exercise, with only a modest increase toward baseline values towards the end (Fig. 5*C*). During the HEC, arterial FFA concentrations were initially ∼0.5 mmol/L at baseline after which it was suppressed to negligible levels, consistent with insulin-mediated inhibition of lipolysis. FFA exchange iAUC did not differ across conditions ($P = 0.952$), with values around zero in all four conditions, indicating neither net uptake nor release (Fig. 6*C*). In the saline condition, arterial lactate concentrations were stable at rest (∼1.0–1.5 mmol/L), rose at exercise onset peaking at approximately 5.5 mmol/L, and returned to resting levels during recovery (Fig. 5*D*). During the HEC, arterial lactate concentrations followed a similar pattern. Lactate exchange iAUC reflected modest net uptake under resting conditions but shifted to marked net release during exercise in both the saline and hyperinsulinaemic conditions ($P = 0.00341$) (Fig. 6*D*).

Skeletal muscle perfusion

Prior to exercise, perfusion values were similar across all conditions, ranging from 3.4 to 3.7 mL/100 g/min (exercise effect: $P = 0.718$; insulin effect: $P = 0.791$; interaction: $P = 0.942$) (Fig. 7*A*). Following exercise, perfusion was higher in the exercised leg than the non-exercised leg with and without insulin (non-exercise + saline: 2.8 ± 1.1; exercise + saline: 10.5 ± 4.2; insulin + non-exercise: 2.3 ± 1.3; insulin + exercise: 11.7 ± 6.1 mL/100 g/min, exercise effect: $P = 0.00103$; insulin effect: $P = 0.920$; interaction: $P = 0.569$) (Fig. 7*B*).

One-legged exercise workload

Power output during the one-legged exercise protocol was comparable between visit 1 and visit 2 (30.5 (26.2–37.4)

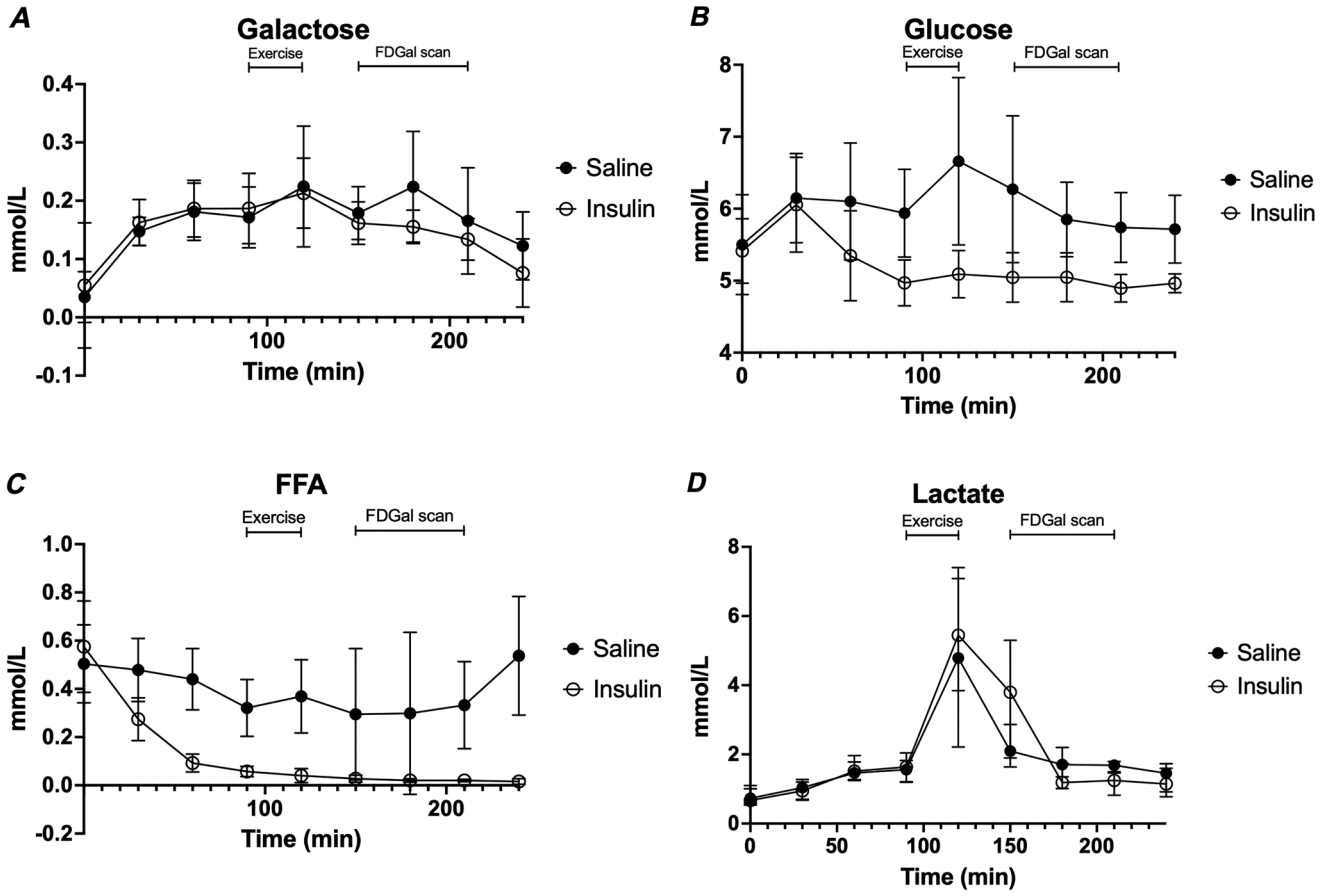

Figure 5. Arterial concentrations of metabolites
Galactose (*A*), glucose (*B*), FFAs (*C*) and lactate (*D*), throughout the study day under saline and insulin stimulation conditions. Data are expressed as means with SD (galactose, FFA and glucose) and median with interquartile range (lactate), $n = 8$. Abbreviations: FDGal, 2-[^{18}F]fluoro-2-deoxygalactose; FFAs, free fatty acids.

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vs. 34.1 (29.7–35.9) W, $P = 0.250$) and did not differ either when divided into the saline and insulin days (33.6 (29.2–37.4) *vs.* 32.0 (26.2–35.8) W, $P = 0.312$).

Discussion

The present study provides *in vivo* evidence that human skeletal muscle can take up galactose. Using [^{18}F]FDGal PET in combination with a one-legged knee-extension ergometer, we demonstrate that both high-intensity exercise and insulin markedly increase galactose uptake, with an additive effect when combined. These findings challenge the prevailing view that galactose must be converted to glucose in the liver prior to peripheral utilisation. This view stems largely from studies conducted under resting conditions, where research on galactose metabolism has typically focused on its hepatic conversion to glucose or glycogen (Fried et al., 1996; Gannon et al., 2001). The same pattern holds post-exercise, where galactose and fructose have been shown to preferentially support hepatic glycogen restoration. Combining maltodextrin with either galactose or fructose has been shown to double post-exercise liver glycogen synthesis rates compared with maltodextrin plus glucose (Décombaz et al., 2011). Conversely, during recovery from exhaustive exercise, glucose ingestion resulted in greater skeletal muscle glycogen resynthesis than either galactose alone or a galactose–glucose mixture, which produced similarly lower rates of muscle glycogen repletion (Podlogar et al., 2023). These findings have been interpreted as galactose being a less effective substrate for post-exercise muscle glycogen synthesis because it must first undergo hepatic conversion to glucose, thereby delaying its availability during the early recovery period. However, this interpretation is challenged by evidence from the same study

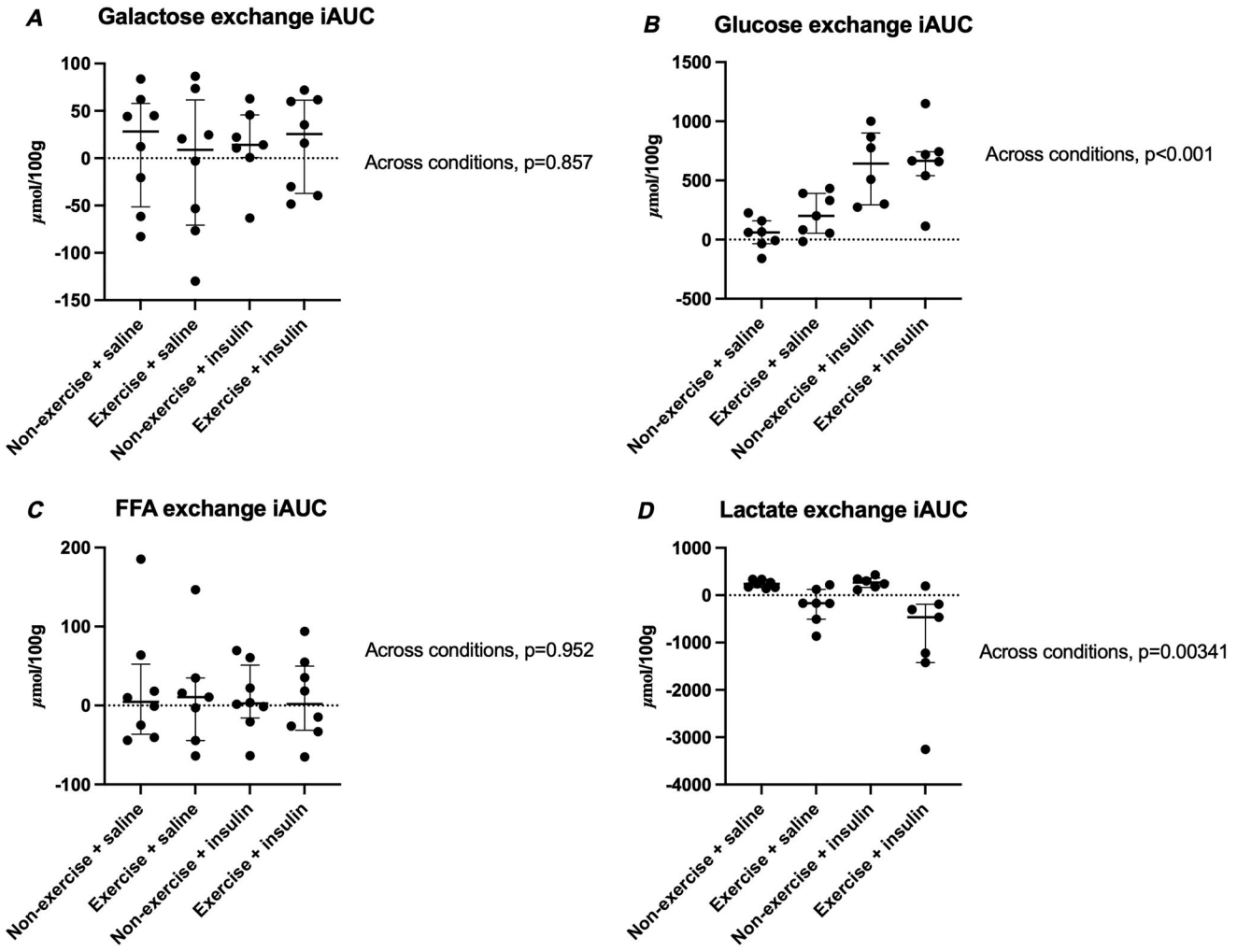

Figure 6. The iAUC of metabolites
Galactose (*A*), glucose (*B*), FFA (*C*) and lactate (*D*), exchange across four treatment conditions: non-exercise + saline, exercise + saline, non-exercise + insulin, and exercise + insulin. Data are expressed as medians with interquartile ranges, $n = 8$. Abbreviations: FFA, free fatty acids; iAUC, incremental area under the curve.

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demonstrating expression of the key Leloir pathway enzymes including galactokinase, galactose-1-phosphate uridylyltransferase, and UDP-galactose 4-epimerase in human skeletal muscle, indicating an intrinsic capacity for direct galactose metabolism (Podlogar et al., 2023). Our findings provide *in vivo* evidence that human skeletal muscle can directly take up galactose and that this uptake is stimulated by both exercise and insulin.

High-intensity one-legged exercise increased galactose uptake approximately four- to fivefold in the exercised leg during saline infusion, whereas hyperinsulinaemia increased uptake more than 10-fold in resting muscle and further augmented uptake in exercised muscle, consistent with an additive effect. Examining the underlying mechanisms of galactose uptake, exercise increased the plasma-to-tissue influx of galactose under both saline and insulin conditions, whereas insulin alone had no detectable effect on K1. While k2 was largely stable across conditions, a lower efflux was observed in the exercised leg during insulin stimulation compared with exercise with saline. This reduction is concurrent with the insulin-stimulated increase in k3, observed in both the exercised and rested leg, which likely reflects enhanced galactokinase activity whereby conversion of intracellular galactose to galactose-1-phosphate reduces the free intracellular galactose available to drive efflux. Taken together, these findings point to k3 as an important determinant of galactose uptake in skeletal muscle, similar to observations in the liver (Sørensen, Mikkelsen et al., 2011). Mechanistically, exercise and insulin therefore appear to exert complementary effects, with exercise primarily increasing galactose influx via enhanced muscle perfusion and a modest secondary contribution through galactokinase activity, whereas insulin acts predominantly by stimulating phosphorylation and intracellular trapping. Since both exercise and insulin stimulate glucose uptake, mainly attributed to GLUT4 translocation to the plasma membrane, galactose uptake was expected to be regulated in the same way. GLUT4 is the dominant insulin- and contraction-responsive hexose transporter in mature skeletal muscle and has lower affinity for galactose than for glucose (Rees & Holman, 1981), whereas GLUT1 is constitutively expressed, but works independently of insulin or contraction, also with lower affinity for galactose than glucose (Holman, 2020). The observed galactose uptake pattern is more consistent with GLUT1 mediating basal galactose entry, with insulin instead acting as a downstream metabolic pull via galactokinase, rather than with insulin-stimulated GLUT4 translocation. Exercise, in contrast, increased galactose uptake through both a threefold increase in muscle perfusion, which mirrors observations for FDG extraction under similar conditions (Nuutila et al., 2000), and an increase in transport capacity, as reflected by a higher PS, consistent with contraction-mediated GLUT4 recruitment. GLUT3, GLUT10 and GLUT12 remain possible additional contributors, but current evidence does not support a major role for any of these in skeletal muscle galactose uptake (Chadt & Al-Hasani, 2020; Dawson et al., 2001; McMillin et al., 2017).

The AV differences were measured to complement PET-derived estimates of galactose uptake. However, arterial galactose concentrations during galactose infusion remained low (∼0.2 mmol/L), resulting in minimal AV differences. Consequently, calculated galactose uptake based on AV differences was close

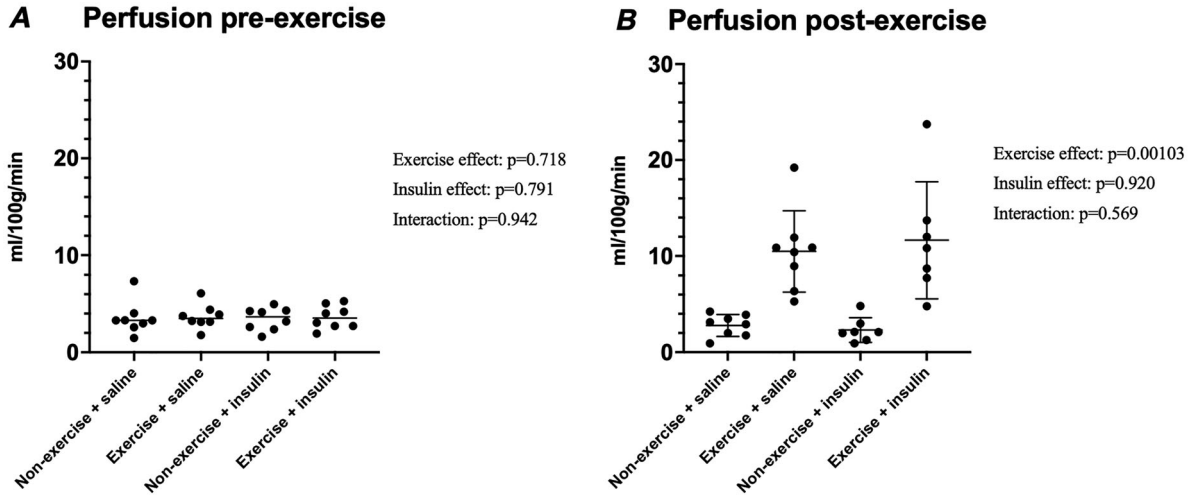

Figure 7. Perfusion measured in the quadriceps muscles measured with [^{15}O]H_2O PET
A, pre-exercise perfusion did not differ between legs or conditions for all four conditions. *B*, post-exercise perfusion was higher in the exercised right leg than the non-exercised left leg during both saline and insulin infusion conditions. Data are means with SD; n = 8 for saline conditions, n = 7 for hyperinsulinaemic conditions due to one failed [^{15}O]H_2O PET scan. Abbreviations: PET, positron emission tomography.

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to zero, indicating negligible net galactose uptake across skeletal muscle. Thus, although PET-measured galactose uptake increased markedly in response to exercise and insulin stimulation, these findings must be considered in relation to the low circulating galactose concentrations achieved in the present study. In line with this, back-calculation of expected AV differences, obtained by dividing absolute [^{18}F]FDGal uptake values by perfusion measurements, yielded estimated concentration gradients of ∼0.001–0.01 mmol/L. The absence of detectable galactose AV differences should therefore be interpreted as a methodological limitation rather than evidence of negligible or absent galactose uptake. The quantitative physiological relevance of skeletal muscle galactose uptake therefore remains uncertain. This is important when extrapolating to oral galactose ingestion in a clinical setting, where most galactose can undergo hepatic first-pass metabolism. Nevertheless, the observed uptake pattern measured with PET closely parallels the well-established insulin- and contraction-mediated stimulation of glucose uptake (Bonadonna et al., 1993; Sylow et al., 2017), suggesting that galactose and glucose uptake are regulated similarly in skeletal muscle.

As an estimation of whole-body skeletal muscle galactose uptake under postprandial conditions, the insulin-stimulated uptake rate measured in non-exercising muscle (0.08 μmol/100 g/min) was applied to an estimated total skeletal muscle mass of 27 kg of the participants. This mass was derived from mean participant body weight combined with an age-appropriate skeletal muscle fraction of 34% of body mass, based on reference data for men aged 60–69 years (Janssen et al., 2000). The resulting whole-body skeletal muscle galactose uptake was approximately 0.02 mmol/min, representing ∼2% of the galactose infusion rate of 1 mmol/min. However, this must also be interpreted in the context of the observed low plasma galactose concentrations, as hepatic extraction and thereby galactose availability, as well as muscle uptake via facilitated diffusion (Klip et al., 1996), are all dependent on the concentration gradient. Validation studies in pigs have demonstrated a single-pass hepatic extraction fraction of 0.43 (Sørensen et al., 2008), where native galactose competes with the [^{18}F]FDGal for galactokinase in a concentration-dependent manner. In humans, at ∼3 mmol/L galactose the hepatic extraction fraction decreases to 0.02, causing the tracer to bypass the liver thereby rendering extrahepatic metabolism quantitatively relevant (Sørensen, Mikkelsen et al., 2011). Notably, as galactose is normally consumed alongside glucose in the form of lactose, its co-ingestion with glucose markedly blunts the systemic galactose response, partly through increased first-pass hepatic extraction (Sunehag & Haymond, 2002). Oral ingestion of galactose at doses of 0.5–0.7 g/kg body weight have been demonstrated to result in peak plasma galactose concentrations of approximately 1.7–2.6 mM within 60 min, although with considerable interindividual variation reaching up to 4.6 mM (Coss-Bu et al., 2009; Williams et al., 1983). These doses are comparable to the galactose load consumed in a dairy-containing meal in a Western diet. The true uptake of galactose into skeletal muscle may therefore be considerably greater than the estimates in this study.

The use of [^{18}F]FDGal to measure galactose metabolism

Although [^{18}F]FDGal is a structural analogue of galactose, it does not metabolically behave exactly like native galactose. After cellular uptake, [^{18}F]FDGal is phosphorylated by galactokinase to [^{18}F]FDGal-1-phosphate, a rate-limiting step in galactose metabolism (Sørensen et al., 2008). However, galactokinase has a slightly higher affinity for native galactose than for [^{18}F]FDGal (Sørensen et al., 2008; Thomas et al., 1974). Converting tracer-derived measurements to true galactose uptake therefore requires an LC, a correction factor accounting for kinetic differences between tracer and native substrate across all steps from membrane transport to irreversible intracellular trapping, estimated at 0.13 in human liver (Sørensen, Mikkelsen et al., 2011). Hepatic [^{18}F]FDGal uptake is determined predominantly by galactokinase activity, and the low hepatic LC mainly reflects differences in intracellular phosphorylation between [^{18}F]FDGal and native galactose (Sørensen, Mikkelsen et al., 2011). In contrast, skeletal muscle uptake is also regulated by GLUT4 translocation (Vendelbo et al., 2014), whereby the relative contributions of transport and phosphorylation differ fundamentally from liver, rendering the hepatic LC non-transferable. A conservative LC of 1 was therefore applied, such that PET-derived estimates represent minimum values of skeletal muscle galactose uptake. A methodological advantage of the lower affinity of [^{18}F]FDGal for galactokinase is that tracer metabolism is slow, limiting conversion of [^{18}F]FDGal to [^{18}F]FDG via the Leloir pathway. Hepatically produced [^{18}F]FDG could theoretically be released into the systemic circulation and subsequently taken up by skeletal muscle independently of galactose metabolism, thereby confounding tissue-specific uptake. However, the absence of detectable plasma [^{18}F]FDGal metabolites 90 min after tracer administration confirms that this conversion is negligible (Sørensen et al., 2008), indicating that the signal in skeletal muscle mostly reflects [^{18}F]FDGal uptake. The tracer can thus be considered to reflect irreversible intracellular trapping across the 60 min PET acquisition in this study.

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Limitations

Several limitations of the present study should be acknowledged. First, current LC estimates are derived from hepatic measurements, and whether these translate to skeletal muscle remains to be established. Further studies examining the competitive kinetics of uptake and phosphorylation in skeletal muscle are needed to characterise the metabolic capacity of this tissue for galactose handling. Second, intravenous galactose administration circumvents intestinal absorption and hepatic first-pass handling, and our findings therefore do not directly reflect the physiological response to oral galactose intake. Third, the small sample size limits statistical power to detect interaction effects, such as the exercise–insulin interaction on galactose uptake, and larger studies are needed to confirm the nature of this combined effect. Fourth, our exercise protocol was set to high intensity to induce glycogen depletion, yielding mean arterial lactate concentrations of 5.5 mmol/L. This was chosen to maximise the stimulus for galactose uptake in skeletal muscle after exercise. Whether galactose uptake is similarly stimulated during or after lower-intensity exercise, which is more representative of what is achievable for individuals with cardio-metabolic conditions, remains an important question for future studies. Finally, regulations on radiation exposure in clinical trials restricted eligibility to older individuals, resulting in a mean age of 68 years, and only men were successfully recruited. These factors limit the generalisability of the findings to women and to populations with differing age-related metabolic and disease profiles.

Conclusion

This study demonstrates that human skeletal muscle is capable of directly taking up galactose, and this uptake is strongly stimulated by both exercise and insulin. This challenges the prevailing view that galactose must first undergo hepatic conversion before peripheral utilisation and highlights a potential role for galactose in skeletal muscle carbohydrate metabolism. Galactose may therefore be a favourable carbohydrate in settings where glycaemic stability is a clinical priority, such as in individuals with diabetes. Although the present study provides proof of concept for direct galactose uptake by skeletal muscle, further studies are required to determine whether galactose is incorporated into skeletal muscle glycogen to a physiologically meaningful extent.

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Additional information

Data availability statement

All original data that support the findings of this study are available from the corresponding author, T.V.L., upon request.

Competing interests

T.V.L. is partner in a sports nutrition company. The other authors declare no conflicts of interest.

Author contributions

The study was conducted at the Department of Nuclear Medicine, Aarhus University Hospital and Steno Diabetes

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Centre Aarhus, Denmark. T.V.L., R.F.J., M.V., M.S., G.A.W., D.S.R., L.C.G. and E.S. contributed to the conception of the work. T.V.L., A.H.J.M. and C.T. contributed to the data acquisition. T.V.L., M.G.B.P., M.S., D.S.R. and E.S. contributed to the data analysis. All authors contributed to the data interpretation. T.V.L. and E.S. drafted the manuscript. All authors critically revised the manuscript for important intellectual content. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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No generative AI tools were used in the preparation of this manuscript.

Keywords

exercise, galactose metabolism, hyperinsulinaemic–euglycaemic clamp, positron emission tomography

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