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APPENDIX

To derive the glucose model in terms of concentration, the model is formulated in terms of mass. The mass representation is shown in Fig.1. The mass balance equations are:

$$\begin{aligned} \dot{q}_x(t) &= k_1 q_p(t) - (k_2 + k_3) q_x(t) + k_4 q_e(t) & \quad q_x(0) = 0 \\ \dot{q}_e(t) &= k_3 q_x(t) - (k_4 + k_5) q_e(t) & \quad q_e(0) = 0 \\ \dot{q}_m(t) &= k_5 q_e(t) - k_6 q_m(t) & \quad q_m(0) = 0 \end{aligned} \tag{1}$$

where q_p, q_x, q_e are the glucose amounts in plasma, extra-cellular space, and tissue , respectively, and q_m is the amount of phosphorylated glucose in tissue.

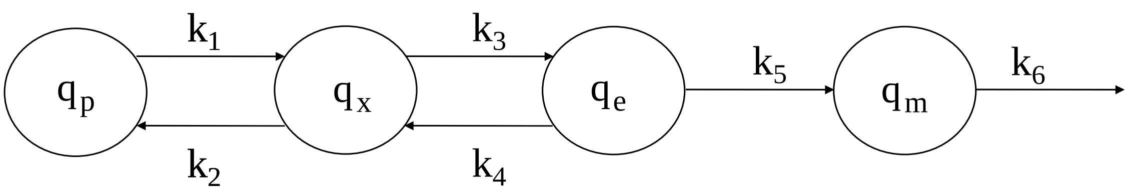

Fig.1.

Denoting V_p, V_x, V_t as the plasma, extra-cellular and tissue volumes respectively, the equations are:

$$\begin{aligned} V_x \dot{C}_x(t) &= k_1 V_p C_p(t) - (k_2 + k_3) V_x C_x(t) + k_4 V_t C_e(t) & \quad V_x C_x(0) = 0 \\ V_t \dot{C}_e(t) &= k_3 V_x C_x(t) - (k_4 + k_5) V_t C_e(t) & \quad V_t C_e(0) = 0 \\ V_t \dot{C}_m(t) &= k_5 V_t C_e(t) - k_6 V_t C_m(t) & \quad V_t C_m(0) = 0 \end{aligned} \tag{2}$$

Dividing by V_t:

$$\begin{aligned} \frac{V_x}{V_t} \dot{C}_x(t) &= k_1 \frac{V_p}{V_t} C_p(t) - (k_2 + k_3) \frac{V_x}{V_t} C_x(t) + k_4 C_e(t) & \quad \frac{V_x}{V_t} C_x(0) = 0 \\ \dot{C}_e(t) &= k_3 \frac{V_x}{V_t} C_x(t) - (k_4 + k_5) C_e(t) & \quad C_e(0) = 0 \\ \dot{C}_m(t) &= k_5 C_e(t) - k_6 C_m(t) & \quad C_m(0) = 0 \end{aligned} \tag{3}$$

Defining:

$$\begin{aligned} C_i(t) &= \frac{V_x}{V_t} C_x(t) \\ K_1 &= k_1 \frac{V_p}{V_t} \end{aligned} \tag{4}$$

The mass balance equations in terms of concentration can be written (Fig.2):

$$\begin{aligned} \dot{C}_i(t) &= K_1 C_p(t) - (k_2 + k_3) C_i(t) + k_4 C_e(t) & \quad C_i(0) = 0 \\ \dot{C}_e(t) &= k_3 C_i(t) - (k_4 + k_5) C_e(t) & \quad C_e(0) = 0 \\ \dot{C}_m(t) &= k_5 C_e(t) - k_6 C_m(t) & \quad C_m(0) = 0 \end{aligned} \tag{5}$$

where:

$C_i(t) = \frac{V_x}{V_t} C_x(t) = \frac{q_x(t)}{V_t}$ is the glucose extra-cellular concentration normalized to intracellular volume;

$C_e(t) = \frac{q_e(t)}{V_t}$ is the intracellular glucose concentration, and

$C_m(t) = \frac{q_m(t)}{V_t}$ is the intracellular concentration of phosphorylated glucose

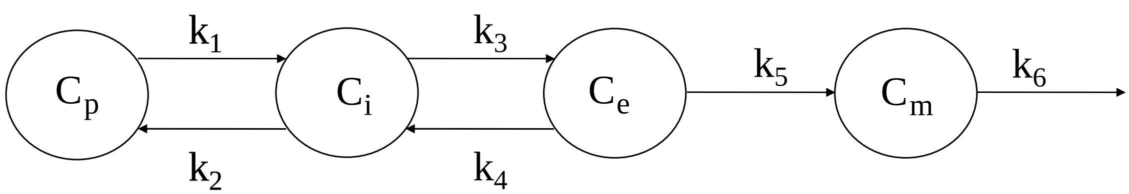

Fig.2

Considering steady state conditions, wherein:

$$\begin{aligned} 0 &= K_1 C_p - (k_2 + k_3) C_i + k_4 C_e \\ 0 &= k_3 C_i - (k_4 + k_5) C_e \\ 0 &= k_5 C_e - k_6 C_m \end{aligned} \tag{6}$$

one obtains:

$$\begin{aligned} C_i &= \frac{K_1 (k_4 + k_5)}{k_2 k_4 + k_2 k_5 + k_3 k_5} C_p \\ C_e &= \frac{K_1 k_3}{k_2 k_4 + k_2 k_5 + k_3 k_5} C_p \\ C_m &= \frac{k_5}{k_6} \times \frac{K_1 k_3}{k_2 k_4 + k_2 k_5 + k_3 k_5} C_p \end{aligned} \tag{7}$$

Since k_6 is not estimable from the triple tracer PET study, only C_i and C_e can be calculated assuming Cp = plasma glucose. However, only C_e has a direct physiological meaning while C_i is a value normalized to tissue volume.

The model allows for the calculation of two operational distribution volumes, one related to the extra-cellular (Vec) and one related to the intracellular (Vic) space:

$$\begin{aligned} V_{ec} &= \frac{C_i}{C_p} = \frac{K_1 (k_4 + k_5)}{k_2 k_4 + k_2 k_5 + k_3 k_5} \\ V_{ic} &= \frac{C_e}{C_p} = \frac{K_1 k_3}{k_2 k_4 + k_2 k_5 + k_3 k_5} \end{aligned} \tag{8}$$

From Eq.8:

$$\frac{V_{ic}}{V_{ec}} = \frac{C_e}{C_i} = \frac{q_e}{V_t} \frac{V_t}{q_x} = \frac{q_e}{q_x} = \frac{k_3}{k_4 + k_5} \tag{9}$$

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Eq.9 gives the ratio of the "true" glucose mass in the intracellular space to "true" glucose mass in the extra-cellular space.

Supplementary Table 1. Kinetic Parameters for [^{18}F]FDG.

	Basal			Insulin Stimulation		
	NW	OB	T2D	NW	OB	T2D
k_1 (ml/ml per min)	0.025 ± 0.002 (2 ± 0.19%)	0.028 ± 0.005 (2 ± 0.22%)	0.021 ± 0.002 (3 ± 0.24%)	0.019 ± 0.001 (4 ± 0.62%)	0.027 ± 0.004 (4 ± 0.76%)	0.020 ± 0.001 (3 ± 0.45%)
k_2 (min^{-1})	0.170 ± 0.012 (4 ± 0.45%)	0.223 ± 0.044 (5 ± 0.72%)	0.140 ± 0.014 (6 ± 0.76%)	0.081 ± 0.023 (46 ± 14.80%)	0.206 ± 0.064 (12 ± 1.70%)	0.159 ± 0.019 (6 ± 0.47%)
k_3 (min^{-1})	0.015 ± 0.001 (17 ± 2.56%)	0.027 ± 0.008 (25 ± 2.50%)	0.014 ± 0.001 (31 ± 4.48%)	0.184 ± 0.025 (37 ± 11.43%)	0.114 ± 0.032 (13 ± 3.79%)	0.037 ± 0.006* (12 ± 2.60%)
k_4 (min^{-1})	0.013 ± 0.002 (84 ± 8.86%)	0.047 ± 0.023 (61 ± 10.96%)	0.022 ± 0.005 (86 ± 8.64%)	0.011 ± 0.003 (110 ± 39.56%)	0.012 ± 0.008 (114 ± 39.73%)	0.020 ± 0.004 (44 ± 8.98%)
k_5 (min^{-1})	0.025 ± 0.005 (81 ± 9.77%)	0.031 ± 0.005 (37 ± 13.04%)	0.031 ± 0.006 (33 ± 6.50%)	0.039 ± 0.009 (62 ± 15.04%)	0.039 ± 0.010 (54 ± 13.29%)	0.035 ± 0.002 (16 ± 3.26%)
V_{tot} (ml/ml)	0.197 ± 0.015 (22 ± 4.29%)	0.165 ± 0.012 (10 ± 3.42%)	0.182 ± 0.006 (9 ± 2.01%)	0.455 ± 0.050 (26 ± 6.96%)	0.431 ± 0.124 (38 ± 11.28%)	0.190 ± 0.011 (7 ± 1.28%)
V_{ec} (ml/ml)	0.139 ± 0.004 (3 ± 0.36%)	0.122 ± 0.010 (3 ± 0.52%)	0.143 ± 0.007 (4 ± 0.57%)	0.090 ± 0.009 (30 ± 8.93%)	0.102 ± 0.011 (7 ± 1.24%)	0.112 ± 0.007* (3 ± 0.27%)
V_{ic} (ml/ml)	0.066 ± 0.013 (67 ± 4.29%)	0.043 ± 0.003 (32 ± 10.31%)	0.040 ± 0.005 (33 ± 6.61%)	0.365 ± 0.053 (60 ± 14.77%)	0.329 ± 0.129 (52 ± 12.70%)	0.078 ± 0.013* (16 ± 3.26%)

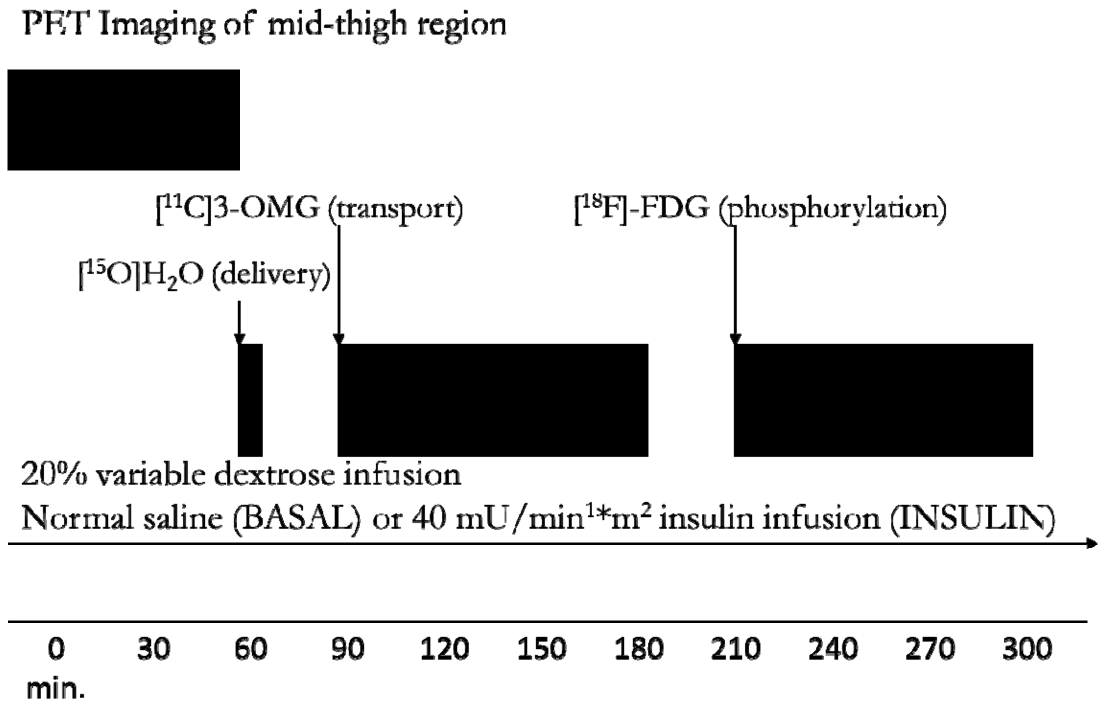
Supplementary Table 2. Kinetic Parameters for Glucose Kinetics.

	Basal			Insulin Stimulation		
	NW	OB	T2D	NW	OB	T2D
k_5 (min^{-1})	0.058 ± 0.015 (34 ± 11.65%)	0.050 ± 0.005 (27 ± 3.75%)	0.040 ± 0.007 (21 ± 2.26%)	0.250 ± 0.041 (62 ± 15.35%)	0.199 ± 0.010 (29 ± 6.98%)	0.085 ± 0.018* (45 ± 5.91%)
V_{tot} (ml/ml)	0.149 ± 0.007 (3 ± 0.75%)	0.149 ± 0.008 (3 ± 0.24%)	0.160 ± 0.013 (2 ± 0.34%)	0.162 ± 0.065 (16 ± 3.55%)	0.120 ± 0.010 (10 ± 2.77%)	0.175 ± 0.029 (7 ± 1.27%)
V_{ec} (ml/ml)	0.125 ± 0.005 (3 ± 0.38%)	0.127 ± 0.007 (3 ± 0.66%)	0.133 ± 0.010 (3 ± 0.36%)	0.122 ± 0.013 (14 ± 3.05%)	0.089 ± 0.007 (10 ± 2.34%)	0.127 ± 0.008† (4 ± 0.62%)
V_{ic} (ml/ml)	0.024 ± 0.004 (31 ± 11.33%)	0.021 ± 0.002 (26 ± 3.42%)	0.028 ± 0.006 (20 ± 2.02%)	0.040 ± 0.063 (59 ± 14.91%)	0.031 ± 0.006 (28 ± 6.21%)	0.049 ± 0.024 (42 ± 6.57%)
C1	0.048 ± 0.007 (7 ± 0.55%)	0.050 ± 0.008 (6 ± 0.44%)	0.044 ± 0.003 (5 ± 0.55%)	0.470 ± 0.075 (7 ± 1.03%)	0.315 ± 0.073 (6 ± 0.72%)	0.121 ± 0.025‡ (7 ± 0.50%)
C2	0.598 ± 0.065 (15 ± 3.02%)	0.649 ± 0.034 (14 ± 4.70%)	0.618 ± 0.049 (12 ± 1.58%)	0.438 ± 0.071 (11 ± 2.63%)	0.612 ± 0.077 (5 ± 1.23%)	0.709 ± 0.064‡ (8 ± 1.72%)
C3	0.355 ± 0.071 (31 ± 11.37%)	0.301 ± 0.033 (28 ± 4.10%)	0.338 ± 0.049 (23 ± 2.54%)	0.092 ± 0.097 (55 ± 14.70%)	0.074 ± 0.009 (28 ± 5.80%)	0.169 ± 0.059 (50 ± 8.70%)

*****$p<0.05$ vs. NW and OB, †$p<0.05$ vs. OB, ‡$p<0.05$ vs. NW

SUPPLEMENTARY DATA

Supplementary Figure 1. Study Design



Radioactive tracers are injected sequentially as above, after the dextrose infusion (and insulin infusion in the INSULIN studies) is started. The dynamic PET imaging time period of each particular tracer is shown in the black boxes