Does IMCL Correlate with Peripheral or Hepatic or Total Insulin Sensitivity?

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Introduction

Intramyocellular lipids (IMCL) in the soleus muscle of human legs have been shown, using ^{1}H spectroscopy, to be negatively correlated with insulin sensitivity (IS) [1-3]. However, this correlation has mainly been reported against a measure of total body glucose utilisation (M-value) using the gold standard method of assessing IS – the hyperinsulinaemic euglycaemic clamp. Other methods differ in their sensitivity weighting to peripheral and hepatic IS and here we have compared IMCL measurements in healthy human control subjects with their corresponding measurements of IS from hepatic, peripheral and total components of the clamp, meal glucose tolerance test (MGTT), and homeostatic model (HOMA).

Methods

General

Twelve healthy volunteers (8 male, 4 female), aged 18 to 35 years, with normal body mass index (20 to 25 kg/m^2), each undertook a ^{1}H spectroscopy scan to determine IMCL, a hyperinsulinaemic clamp, and an MGTT, with each test separated by a minimum of 1 week. The clamp and MGTT were performed following an overnight fast and blood samples taken prior to each test to allow fasting glucose and insulin levels to be determined for the HOMA measurement of IS.

IMCL measurement

A ^{1}H spectrum was obtained from a voxel, of cube length 1.5 cm, in the soleus muscle of the right leg using PRESS (Point Resolved Spectroscopy) on a Bruker 3.0 T scanner. Gradient echo images in three orthogonal directions were used for localisation of the voxel, avoiding fasciae lines and visible fat on the images. An accurate shim was obtained by shimming on a 6 cm cube, centred on the voxel, using FASTMAP [4], prior to shimming the individual voxel. Voxel profile and water suppression, using CHESS (Chemical Shift Selective), were optimised and data acquired with a TE = 35 ms, TR = 5 s and 64 averages taken. In 4 out of the 12 subjects data was also taken in a second voxel. The original localisation scan was repeated at the end of the experiment to check for any displacement of the leg during the scan. The spectra were line broadened prior to fourier transform and then phase and baseline corrected. The water peak was calibrated to 4.7 ppm and line fitting performed, in the frequency domain, using a 50/50 Lorentzian/Gaussian line shape and incorporation of prior knowledge. IMCL was quantified by comparing the area of the resonance at 1.3 ppm (intracellular triglyceride methylene groups) with that of creatine at 3.0 ppm.

Hyperinsulinaemic clamp

A 1-step hyperinsulinaemic, euglycaemic clamp was performed between 0800 and 1300 hrs, using [6,6^{2}H$_2$] glucose. Plasma enrichment was then used to determine baseline (endogenous hepatic glucose production (Ra)) and insulin stimulated glucose turnover (peripheral glucose utilisation (Rd)), using the Steele models for the non-steady state modified for use with stable isotopes [5]. From these a measure of hepatic, peripheral and total IS was calculated.

MGTT

In the MGTT, glucose is orally administered and the kinetics of plasma glucose then interpreted in terms of the minimal model [6]. Volunteers were given 75g of glucose (as a suspension) and their blood was then sampled regularly over the following few hours. Insulin sensitivity was estimated from the profiles of the plasma glucose and insulin concentrations.

Results

Correlation of IMCL value and IS measured using each technique was assessed using a Spearman's correlation, and the results are shown in Table 1.

	Clamp			MGTT	HOMA	
	Total	Hepatic	Peripheral		Sensitivity	Secretion
IMCL	**-0.71**	-0.42	-0.48	-0.43	**-0.74**	-0.25

Table 1: r-values for correlation of IMCL with IS values from other techniques, with correlations of $p < 0.05$ shown in bold. The units of the clamp and MGTT are $(Lhr^{-1}pM^{-1})^{0.5}$.

Conclusion

A significant negative correlation was found between IMCL and HOMA sensitivity (r = -0.74) and, consistent with the literature [1-3], IMCL and the total clamp (M-value) (r = -0.71). No significant correlation was found with the hepatic component of the clamp, MGTT, nor HOMA secretion, which all have a greater weighting to the hepatic component of IS. There appears to be no significant correlation between IMCL and the peripheral component of the clamp, even though the total clamp was found to strongly correlate with the peripheral component of the clamp ($r = 0.86$, $p < 0.001$).

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Acknowledgements

We thank the Wellcome Trust.