

Effect of an acute hyperinsulinaemic clamp on post-prandial lipaemia in subjects with insulin resistance

E. M. Allister*, A. P. James*, G. F. Watts†, P. H. R. Barrett† and J. C. L. Mamo*

*Curtin University of Technology and †University of Western Australia, Perth, Australia

Abstract

Background Obese, insulin-resistant individuals have raised levels of intestinal and hepatic lipoproteins. Insulin decreases the production of hepatic lipoproteins *in vivo* and so this study aimed to investigate whether an acute hyperinsulinaemic, euglycaemic clamp could correct fasting and post-prandial dyslipidaemia.

Subjects and methods In a randomized, cross-over design, post-prandial lipaemia was compared in subjects infused either with insulin to achieve a steady-state concentration of 100 mU L⁻¹ or with saline. Nine obese (Body Mass Index > 26 kg m⁻²; waist : hip > 1.0) insulin-resistant (Homeostatic Model Assessment score > 2.0) male subjects were given an oral fat load 3 h after the infusions began, and sampling continued for 6 h. Plasma apoB-48, triglyceride and nonesterified fatty acid (NEFA) were measured hourly.

Results Average steady-state serum insulin levels during the hyperinsulinaemic clamp were 123 ± 4.4 mU L⁻¹. A paired analysis showed no net effect of insulin on post-prandial chylomicron metabolism when calculated as the (apoB-48) incremental area under the curve (IAUC). However, there was a trend towards a delay in the apoB-48 peak, consistent with possible changes in the rates of chylomicron biogenesis, lipolysis and/or clearance. Similarly, post-prandial lipaemia (depicted as triglyceride IAUC) was similar for subjects infused with insulin or saline, but the peak post-prandial response was delayed during insulin infusion. The NEFA were rapidly decreased by 83% after 3 h of insulin infusion.

Conclusions In obesity and insulin resistance, short-term changes in plasma insulin do not appreciably exert a regulatory effect on exogenously-derived post-prandial lipoproteins. The data suggest that hyperchylomicronaemia in insulin-resistant subjects is a result of chronic aberrations in insulin-mediated regulation of post-prandial lipid metabolism.

Keywords APOB-48, chylomicron, insulin resistance, obesity.

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Abbreviations: Apo, apolipoprotein; AUC, area under the curve; BMI, body mass index; GIP, gastric inhibitory peptide; HDL, high density lipoprotein; HOMA, homeostatic model assessment; IAUC, incremental area under the curve; IMGD, insulin mediated glucose disposal; LDL, low density lipoprotein; LDL-r, low density lipoprotein receptor; MTP, microsomal triglyceride transfer protein; NEFA, nonesterified fatty acid; VLDL, very low density lipoprotein; W : H, waist : hip ratio.

Division of Health Sciences, Curtin University of Technology (E. M. Allister, A. P. James, J. C. L. Mamo); School of Medicine and Pharmacology, University of Western Australia (G. F. Watts, P. H. R. Barrett), Perth, Australia.

Correspondence to: Prof. John Mamo, ATN Centre for Metabolic Fitness, Division of Health Sciences, Curtin University of Technology, Kent Street, Bentley, Western Australia 6102, Tel.: +61 8 92667232; fax: +61 8 92662958; e-mail: j.mamo@curtin.edu.au

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Introduction

A raised plasma concentration of intestinally derived chylomicrons is suggested to increase the development of atherosclerosis [1–4]. The atherogenicity of chylomicrons is related to both chronic exposure to small remnant particles which can penetrate the arterial wall and be selectively retained (reviewed in [5]) and exaggerated and transient exposure during the post-absorptive state. It has previously been found that viscerally obese, insulin-resistant individuals frequently have elevated plasma levels of fasting and post-prandial chylomicrons and chylomicron remnants in circulation, as measured by plasma apolipoprotein (apoB-48) levels, compared with lean subjects [6,7]. This may partly explain their increased atherogenic risk [8]. It is postulated that resistance to the regulatory effects of insulin is responsible for the raised concentrations of chylomicrons and remnants. Evidence for this comes from clinical studies where insulin

has been shown to regulate low-density lipoprotein receptor (LDL-r) activity, which is the primary clearance mechanism for chylomicron remnants *in vivo* [9]. In addition, *ex vivo* cultures of intestinal enterocytes from insulin-resistant Syrian golden hamsters have shown increased apoB-48 production compared with enterocytes from insulin-sensitive controls [10]. Therefore overcoming insulin resistance should theoretically correct the post-prandial dyslipidaemia in viscerally obese subjects, which was tested in this study by utilizing an acute hyperinsulinaemic, euglycaemic clamp.

Insulin has been shown to critically regulate many aspects of hepatic lipoprotein metabolism, and resistance to its actions results in elevated hepatic very low-density lipoprotein (VLDL) triglyceride levels and apoB-100. Several studies have shown that a hyperinsulinaemic, euglycaemic clamp in fasted humans decreases secretion of VLDL by 50–60% and circulating nonesterified fatty acids (NEFA) by $\leq 95\%$ [11–16]. The inhibition of VLDL secretion may, in part, be owing to reduced substrate availability via a lower flux of NEFA to the liver, as well as a direct effect of insulin on VLDL assembly in the liver [11]. In addition, insulin may increase VLDL catabolism and clearance by stimulating lipoprotein lipase activity [17,18] and LDL-r expression [19]. However, because of potentially divergent effects on LPL in different tissues, it is possible that insulin alone will not acutely impact on chylomicron particle clearance [20,21]. On the other hand, owing to both common production and removal pathways for VLDL and chylomicrons, insulin may also positively regulate chylomicron metabolism in humans [22]. This study used the hyperinsulinaemic, euglycaemic clamp technique [23] to investigate whether acute hyperinsulinaemia attenuates chylomicron and post-prandial lipaemic responses in viscerally obese men. The hypothesis of this study was that acute changes in insulin would modulate the metabolism of chylomicrons in these subjects. Specifically, it was hypothesized that high levels of insulin would suppress fasting and post-prandial plasma chylomicron levels.

Subjects and methods

Subjects

Nine viscerally overweight and obese subjects aged $18 \geq 60$ years were recruited from the general community. All the subjects were screened for suitability and underwent a medical examination. Exclusion criteria included being a current smoker, hypertension, genetic hyperlipidaemia, hyper- or hypothyroidism, proteinuria, liver disease, abnormal electrocardiogram, depression, gastrointestinal problems, allergy to dairy products and apo E genotype (E2/E2 exclusion). Diabetes was excluded based on fasting plasma glucose being greater than 7.0 mmol L^{-1} . Inclusion criteria included insulin resistance as measured by the homeostatic model assessment (HOMA) score > 2.0 , BMI $> 26 \text{ kg m}^{-2}$, visceral obesity as measured by a waist : hip ratio (W : H)

> 1 and a waist circumference $> 100 \text{ cm}$, total cholesterol $< 6 \text{ mmol L}^{-1}$ and triglycerides $> 1.2 \text{ mmol L}^{-1}$. All of the obese subjects included in this study had the metabolic syndrome based on the World Health Organization definition [24]. All subjects provided informed written consent and the Ethics Committee of Royal Perth Hospital, approved the study.

Study design

In a randomized, cross-over study design the subjects were studied on two occasions with a 2-week interval. Subjects underwent an hyperinsulinaemic, euglycaemic clamp which aimed to achieve steady-state insulin at 100 mU L^{-1} and glucose at 5 mmol L^{-1} for a period of 9 h [23]. On the other visit the subjects received a saline infusion for 9 h. Subjects fasted for 12 h before arrival at the metabolic ward. On the day preceding the study, the subjects abstained from alcohol and their evening meal was low in fat ($< 20 \text{ g}$). Subjects were kept in a semi-recumbent position during the study and were allowed to drink water. An in-dwelling cannula was placed in a superficial vein of each antecubital fossa at commencement of the study.

Human insulin, Actrapid 100 IU mL^{-1} , (Novo Nordisk, Sussex, UK), was made up with normal saline and infused at a constant rate ($40 \text{ mU m}^{-2} \text{ min}^{-1}$) via the left cannula. An amount of saline that was approximately equivalent to the sum of the insulin and glucose infused during the insulin clamp visit was infused during their next visit. Blood samples (2 mL) were collected from the right cannula every 10 min to measure plasma glucose by a glucose-oxidase technique (Radiometer Pacific, Copenhagen, Denmark). Plasma glucose concentrations of 5 mmol L^{-1} were maintained by an infusion of 25% glucose at a variable rate via the left cannula.

Venous blood samples were collected from the right arm into tubes containing EDTA for plasma (Vacuette; Greiner Bio-one, Kremsmünster, Austria) or SST for sera (Vacutainer; Becton Dickinson, Oxford, UK) just before commencing the insulin/glucose or saline infusion and at 1-h intervals up to 9 h. Blood samples were separated by centrifuging at approximately 2000 g for 10 min. Plasma was collected for determination of apoB-48, lipids and insulin. Serum was collected for NEFA analysis.

During the control study, normal saline (0.9% sodium chloride) was infused at a rate which resulted in a volume equivalent to the volume of insulin and glucose infused during the hyperinsulinaemic, euglycaemic clamp procedure for each group. For confirmation, the haematocrit values were measured at the end of each perfusion period and were not different between study days.

Oral fat test

Three hours after the commencement of the insulin/saline infusion the subjects consumed a fat-load consisting of 75 mL of cream flavoured with 1 g of chocolate powder

within 1 min, as previously described (fat, 37% w/v; carbohydrate, 3 g; protein, 3 g) [25].

Apolipoprotein B-48 determination, lipids, nonesterified fatty acid and insulin assays

The apoB-48 was quantified using a Western blotting/enhanced chemiluminescence procedure, as previously described [26]. Plasma triglyceride and total cholesterol (Trace Scientific Ltd, Melbourne, Australia) and NEFA (Wako Pure Chemical Industries Ltd, Osaka, Japan) were determined by enzymatic colourimetric kits. Plasma insulin was measured using an ELISA kit (Dako Diagnostics, Kyoto, Japan).

Pre- and post-prandial assessment

The net effect of the insulin infusion on fasting levels of chylomicrons and triglyceride was measured by comparing the gradient of the line in the first 3 h of the saline infusion and insulin clamp. Post-prandial metabolism was quantified by the trapezoid method and was calculated as the area-under-the-curve (AUC) for plasma glucose and total cholesterol. For apoB-48, triglyceride and NEFA, the incremental AUC (IAUC) was calculated between 0–3 h, 0–6 h or 2–6 h and represents the post-prandial AUC corrected for baseline level (at time = 0 or 2 h).

Measurement of insulin resistance

Estimation of the subjects' state of insulin resistance for screening purposes was by calculation of a HOMA score [27]. Use of a HOMA score as a measurement of insulin sensitivity has been validated against a 4-h hyperinsulinaemic, euglycaemic clamp in 115 subjects with varying degrees of glucose tolerance and insulin sensitivity [28]. Insulin-mediated glucose disposal (IMGD) ($\text{mmol kg}^{-1} \text{h}^{-1} \text{mU}^{-1}$) was measured during the hyperinsulinaemic, euglycaemic clamp visit over a 1-h period. The IMGD was measured during the hour preceding the fat-load (2 h after the start of the insulin infusion), as the subjects had reached steady-state insulin levels (Fig. 1a). The volume of glucose infused per hour (mL h^{-1}) was normalized for insulin concentration and body weight and then converted to mmol L^{-1} .

Statistical analysis

Statistical analysis was by parametric methods using SPSS for Windows version 10.0 (SPSS Inc., Chicago, IL). Student's paired *t*-test was used to compare clinical and biochemical characteristics (hyperinsulinaemic, euglycaemic clamp versus saline infusion). Comparisons were made based on IAUC measurements for the biochemical measurements and the time to reach the post-prandial peak.

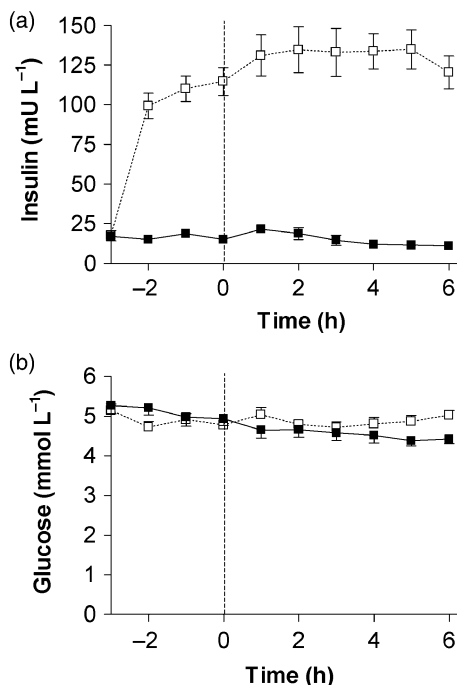


Figure 1 Average serum insulin (a) and plasma glucose (b) concentrations during saline infusion and insulin clamp. The saline (■) or insulin (□) infusions commenced at time-point -3 h and continued for 9 h. At 0-h time point, the subjects consumed 30 g of fat (dotted line on the graph). Values are mean \pm SEM, $n = 9$.

Results

Subject characteristics

The characteristics of the subjects are shown in Table 1. The subjects in this study were insulin resistant (as measured by HOMA) and had an elevated fasting insulin, were hypertriglyceridaemic and had low levels of HDL-cholesterol. Their systolic and diastolic blood pressure (SBP & DBP), total cholesterol, LDL-cholesterol and fasting glucose were normal (Table 1).

Insulin and glucose concentrations during saline infusion or hyperinsulinaemic/euglycaemic clamp

During the hyperinsulinaemic, euglycaemic procedure plasma insulin concentrations were clamped at an average of $123 \pm 4.4 \text{ mU L}^{-1}$ (Fig. 1a). Peak insulin concentrations were reached and then maintained after approximately 2 h of insulin infusion. Plasma insulin levels (AUC) were significantly higher during the insulin infusion compared with the saline infusion ($P < 0.0001$) (Table 2). In addition, the insulin concentrations 1 h after the fat-load were significantly higher (44%) than the zero time point during the saline infusion ($P < 0.001$).

Table 1 Subject characteristics

	Overweight and obese
<i>n</i>	9
Age (years)	46.6 ± 9.9
Weight (kg)	111 ± 6.0
W : H	1.031 ± 0.025
BMI (kg m ⁻²)	35.1 ± 3.3
SBP (mmHg)	130 ± 15.3
DBP (mmHg)	74.4 ± 10.4
TG (mmol L ⁻¹)	1.9 ± 0.7
Cholesterol (mmol L ⁻¹)	4.9 ± 0.9
LDL-cholesterol (mmol L ⁻¹)	3.1 ± 0.8
HDL-cholesterol (mmol L ⁻¹)	0.92 ± 0.12
Fasting Glucose (mmol L ⁻¹)	5.1 ± 0.4
Fasting Insulin (mU L ⁻¹)	22.9 ± 8.0
HOMA	5.1 ± 1.7
IMGD (mmol kg ⁻¹ h ⁻¹ mU ⁻¹)	1.2 ± 0.6

Values are the mean ± SD.

W : H, waist : hip ratio; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; LDL, low density lipoprotein; HDL, high density lipoprotein; HOMA, homeostatic model assessment insulin resistance; IMGD, insulin-mediated glucose disposal.

Average blood-glucose concentrations during the insulin clamp and saline infusion were 4.9 ± 0.05 mmol L⁻¹ and 4.8 ± 0.1 mmol L⁻¹, respectively (Fig. 1b), with no significant differences between the corresponding glucose AUCs (Table 2).

Fasting and post-prandial ApoB-48 responses

There was no effect of acute hyperinsulinaemia on apoB-48 levels during the 3 h before the fat-load (Fig. 2a). The

average change in apoB-48 concentration from time point -3 h to 0 h during the insulin infusion was -1.89 ± 1.44 µg mL⁻¹ and during the saline infusion was -0.65 ± 0.75 µg mL⁻¹ (*P* = 0.51). After consumption of the fat-load (time point = 0 h), plasma apoB-48 peaked on average at 29% above pre-fat-load levels after 3 h and the post-prandial excursion was essentially complete after 6 h on both the saline and insulin days. In addition, the apoB-48 IAUC (0–6 h) was not different during the saline infusion compared with the insulin infusion (Table 2). The apoB-48 IAUC for 0–3 h was 25% lower during the insulin infusion compared with the saline infusion in the obese subjects, but the difference did not reach statistical significance (*P* = 0.3) (Table 2).

Fasting and post-prandial triglyceride responses

Insulin had no effect on the triglyceride levels during the first 3 h of the infusion, as there was no difference in the change in the triglyceride concentration during this period. During the saline infusion the average change in the triglyceride concentration was -0.03 ± 0.09 mmol L⁻¹ and during the insulin infusion it was 0.01 ± 0.05 mmol L⁻¹ (*P* = 0.68) (Fig. 2b). The fat-load was associated with a post-prandial triglyceride response which peaked at 159% at 3 h post-prandially during the saline infusion and at 166% at 4 h during the insulin infusion. Triglyceride levels returned back to near fasting levels at 6 h post-prandially during both the saline and insulin infusions. There was no significant difference in the 6-h triglyceride IAUC after the fat-load during the saline compared with the insulin clamp (*P* = 0.28) (Table 2). Although the IAUC for the full post-prandial period was not affected by insulin, a significantly lower IAUC was observed during the first 3 h following the meal (0–3 h) on the insulin clamp day (*P* < 0.05), indicative of a delayed response (Table 2).

Table 2 Effect of a hyperinsulinaemic, euglycaemic clamp compared with a saline clamp on blood glucose, plasma insulin and post-prandial apoB-48, triglyceride and NEFA

Plasma analyte	Insulin	Saline	<i>P</i> -value
Plasma insulin (mU L ⁻¹ , 9 h)	1060.2 ± 84.7	139.3 ± 20.2	< 0.0001
Blood glucose (mmol L ⁻¹ , 9 h)	43.2 ± 0.8	42.3 ± 1.5	0.62
ApoB-48 (0–6 h) (µg mL ⁻¹ , 6 h)	21.6 ± 6.1	23.3 ± 6.7	0.92
ApoB-48 (0–3 h) (µg mL ⁻¹ , 3 h)	8.73 ± 2.9	6.60 ± 2.9	0.34
Triglyceride (0–6 h) (mmol L ⁻¹ , 6 h)	3.14 ± 0.2	3.84 ± 0.6	0.36
Triglyceride (0–3 h) (mmol L ⁻¹ , 3 h)	1.31 ± 0.2	0.53 ± 0.1	0.05
NEFA (0–6 h) (mmol L ⁻¹ , 6 h)	0.36 ± 0.06	0.54 ± 0.16	0.39
NEFA (2–6 h) (mmol L ⁻¹ , 4 h)	0.62 ± 0.1	0.26 ± 0.1	< 0.01

Values are the means ± SEM.

Significance was *P* < 0.05.

Plasma insulin and blood glucose area-under-the-curve (AUC) measurements over the entire 9 h protocol (-3–6 h). Apo B-48, and triglyceride are incremental AUC over the 6-h post-fat load period or the first 3-h post-fat-load. NEFA are IAUC over the 6-h post-fat-load period (0–6 h) or the last 4-h of fat-load (2–6 h). Student's paired *t*-tests compare insulin with saline in each group.

ApoB-48, apolipoprotein B-48; NEFA, nonesterified fatty acids.

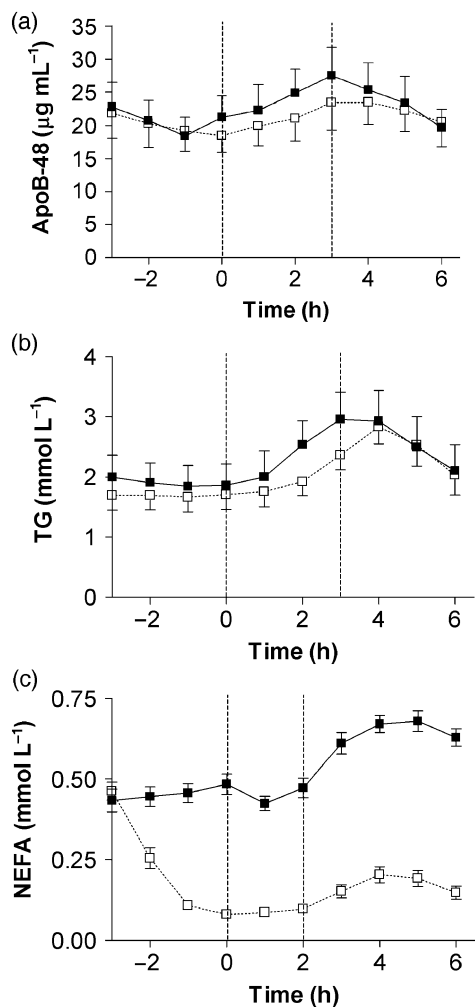


Figure 2 Average plasma apoB-48 (a), plasma triglyceride (TG) (b) and nonesterified fatty acid (NEFA) (c) concentrations during saline infusion and insulin clamp. The saline (■) or insulin (□) infusions commenced at time point -3 h. At 0-h time point the subjects consumed 30 g of fat. Graphs A and B are divided into three sections by dotted lines at 0 h and 3 h as these represent the segments analyzed. Similarly graph C has been divided at 0 h and 2 h as these three segments were analyzed separately for the plasma NEFA concentration. Values are mean \pm SEM, $n = 9$.

Fasting and post-prandial nonesterified fatty acid concentrations

Following 3 h of insulin infusion there was an 83% decrease in plasma NEFA levels; this was significantly different from the 14% increase during saline infusion ($P < 0.0001$) (Fig. 2c). Plasma NEFA concentration during the saline infusion significantly decreased by 12% 1 h after the fat-load (compared with time point 0 h, $P < 0.05$); with a subsequent increase and peak at 5 h ($P < 0.01$ compared with the 0 h time point). During the insulin infusion, there was a significant increase in the NEFA concentration following the fat-load; however, the peak was still 56% lower than fasting

levels and had returned to near pre-fat-load levels by 6 h (68% lower than fasting levels). The post-prandial IAUC for the NEFA response (0–6 h) was 33% lower during the insulin infusion compared with the saline infusion, but the difference was not significant ($P = 0.39$) (Table 2). The IAUC for NEFA from 2–6 h during the insulin infusion was 57% lower than during the saline infusion ($P < 0.01$) (Table 2).

Discussion

This article reports on the effects of acute hyperinsulinaemia on chylomicron metabolism in insulin-resistant subjects under both fasting and post-prandial conditions. The fasting hyperchylomicronaemia and hypertriglyceridaemia in these subjects was not corrected by a 3-h infusion of insulin before the consumption of the fat-load. Furthermore, elevated post-prandial chylomicron (apoB-48) and triglyceride responses were not significantly reduced during the insulin infusion, but the peaks were delayed by the insulin infusion. The lack of effect of insulin on post-prandial chylomicron and triglyceride metabolism is unlikely owing to an inadequate concentration of insulin, as significant physiological effects were observed on plasma NEFA concentrations. Moreover, it is unlikely owing to an inadequate hyperinsulinaemic duration, as the mean plasma residency time for chylomicrons in humans is 5–15 min [29]. Rather, the elevated fasting and post-prandial apoB-48 and triglyceride levels in obese subjects probably represents a chronic dysregulation of chylomicron metabolism that cannot be modulated with a 9-h acute hyperinsulinaemic clamp.

Mitosomal triglyceride transfer protein (MTP) is necessary for the assembly of apoB-48 with lipids to form a secretion competent chylomicron particle [30]. Insulin negatively regulates the MTP expression in hepatic cells via activation of the mitogen-activated protein kinase (MAPK) signalling pathway [31]. Animal models of insulin resistance have an overproduction of intestinally-derived chylomicrons commensurate with an increased expression of MTP [10,32,33]. In this study, insulin infusion did not significantly alter chylomicron homeostasis before or during the absorptive state. However, a delay in the post-prandial response was observed here in insulin-resistant men and reported previously by Harbis et al. in lean healthy subjects [34]. The delay in chylomicron kinetics could be interpreted as being consistent with the concept of an MTP-mediated suppressive effect of insulin on chylomicron biogenesis, but the duration of the insulin infusion may not have been sufficient to maximally inhibit MTP activity, as it is reported that the half-life of MTP is 4.4 days [35].

Insulin directly inhibits apoB-100 secretion from hepatocytes via activation of the MAPK pathway [36] which increases degradation of this otherwise obligatory protein. However, in comparative studies with liver cells, the authors' recently reported that insulin does not decrease the secretion of apoB-48 from human enterocytes [37], suggesting differential regulation of the two apoB isoforms. The clinical

data presented here and that of others investigating VLDL-kinetics [11,12] are consistent with the cell-culture studies, which collectively suggest that the liver is more responsive than the small intestine to acute changes in insulin concentration.

The authors' contend that the delay in chylomicron apoB-48 and triglyceride kinetics induced by hyperinsulinaemia was not a result of the known stimulatory effects of this hormone on adipose tissue lipoprotein lipase or LDL-r expression. The reasoning is that enhancing chylomicron conversion to the high-affinity remnant form, or expression of receptors pivotal for clearance, should have resulted in attenuation of the post-prandial response rather than just a delay. A previous study reported that lipolytic capacity was not limited in insulin-resistant men compared with lean controls [7] and on this basis would not have expected acute hyperinsulinaemia to enhance hydrolytic rates. Moreover, insulin has opposing effects on lipoprotein lipase activity in muscle and adipose tissue [21]. The LDL-r activity is substantially depressed in insulin-resistant subjects and may contribute to the persistently elevated concentration of chylomicron remnants in these subjects [7]. Significantly enhancing receptor activity to subnormal levels via weight loss was not sufficient to ameliorate the aberrations in chylomicron metabolism [38], thus suggesting that full restoration of activity is required. In this study, there was no evidence that acute insulin clamping positively stimulated LDL-r expression, and a delay in chylomicron kinetics is also not consistent with this notion.

Acute hyperinsulinaemia has been found in some studies to decrease the fasting concentration of plasma triglyceride in normal, obese and diabetic individuals [11–16]. In this study, it was found that 3 h of hyperinsulinaemia before the fat-load had no significant effect on triglyceride concentration. While the duration of hyperinsulinaemia may have been insufficient to elicit a response, which is unlikely based on previous studies in lean insulin-sensitive subjects, an effect was observed within 2 h [16]. Rather, resistance to the inhibitory effects of insulin on either hepatic lipoprotein biogenesis of VLDL or failure to stimulate hydrolysis of triglyceride by lipoprotein lipase and/or uptake by receptors are more likely to explain the lack of effect on plasma triglycerides. Malmstrom *et al.* using a similar protocol found that plasma triglycerides were only lowered significantly after 7.5 h of insulin infusion [12].

Differential tissue regulation by insulin was evident by the finding that hyperinsulinaemia rapidly decreased the concentration of NEFA. Indeed, even when subjects were infused with just saline, plasma NEFA concentrations were found to modestly decrease 1 h after the fat-load, commensurate with a small rise in insulin induced by the meal. The observations are consistent with the established suppressive effect of insulin on hormone-sensitive lipase [39]. Such an effect can also account for the observed inhibitory effect on the 2–6-h incremental NEFA response.

Microsomal transfer protein, lipoprotein lipase and the LDL-r are the key proteins that regulate the rate of chylomicron secretion, conversion to the remnant form and rate of internalization. Insulin has profound effects on the expression of each of these enzymes, which will collectively tend

to suppress chylomicron secretion and encourage clearance. The body of evidence suggests that overproduction of chylomicrons and reduced receptor mediated clearance are primarily responsible for the hyperchylomicronaemia and post-prandial dyslipidaemia commonly found in subjects with insulin resistance. Hence, notionally, disturbances in chylomicron kinetics in insulin-resistant subjects could be overcome by either increasing sensitivity to insulin or by exaggerating exposure to the hormone. This study tested the latter and found that an hyperinsulinaemic clamp of 9 h was insufficient to significantly attenuate the post-prandial response or fasting chylomicrons. The findings were consistent with earlier reports *in vivo*, which have explored how insulin sensitivity influences chylomicron kinetics and cell-culture studies that have determined the effects of insulin on protein expression. Collectively, these studies are consistent with the concept that insulin is likely to chronically regulate chylomicron metabolism rather than influence single meal excursions. Chylomicron biosynthesis is constitutive and insulin may be pivotal to establishing basal rates of secretion. While conversion of chylomicrons to remnants does not appear to be rate limiting in insulin-resistant men, expression of high-affinity clearance pathways is, however, substantially depressed. In conclusion, the correction of post-prandial dyslipidaemia in insulin-resistant subjects can probably only be achieved by chronically improving insulin sensitivity.

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