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# Change in Inflammatory Biomarkers in the Postprandial State

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# Hyperglycemia, inflammatory biomarkers, and triglycerides after a high-fat mixed meal in patients with type 2 diabetes

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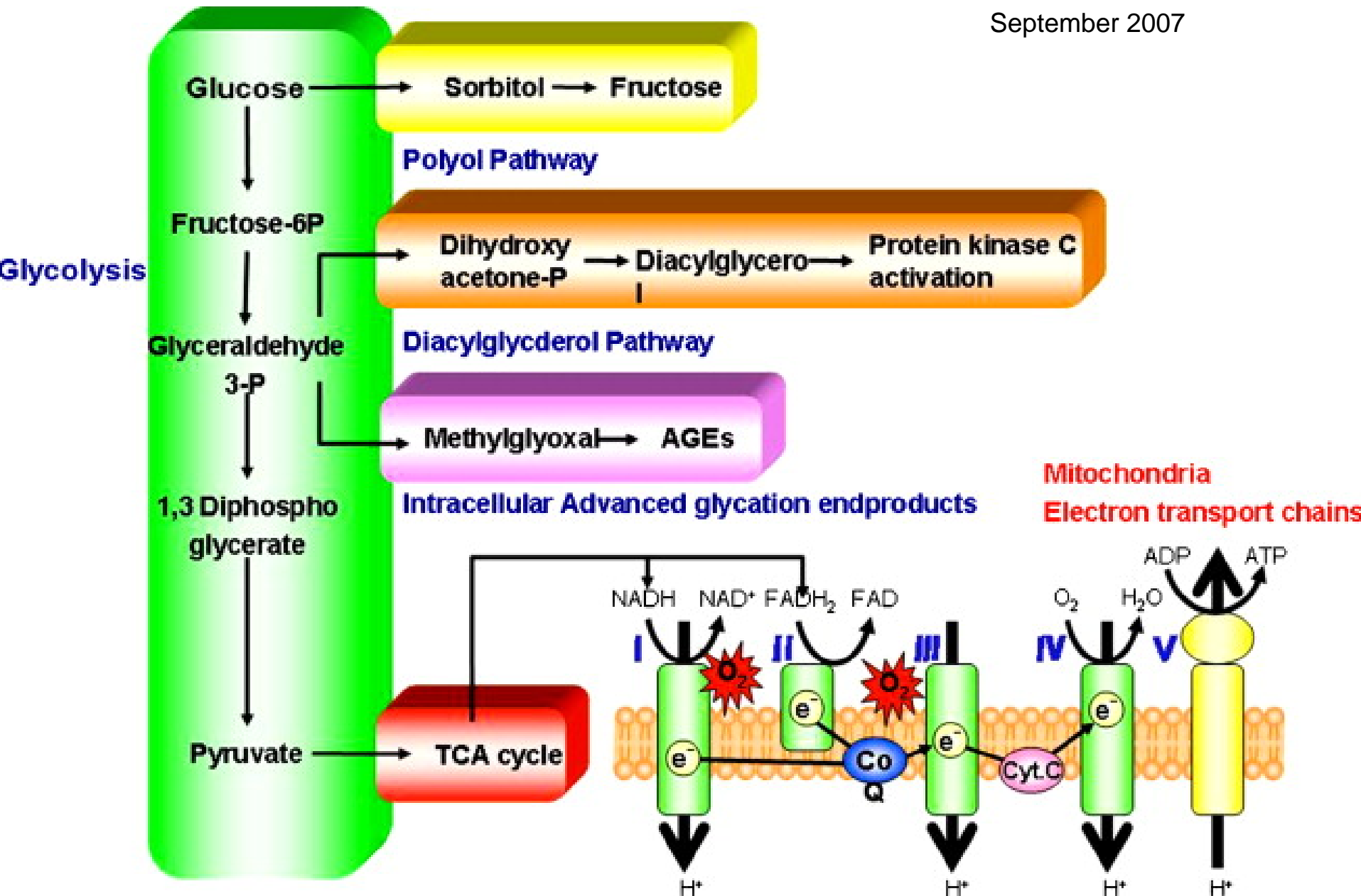
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# Glucose and Tissue Damage

Nishikawa et al.

Diabetes Res and Clin Pract.

September 2007



# Hypotheses

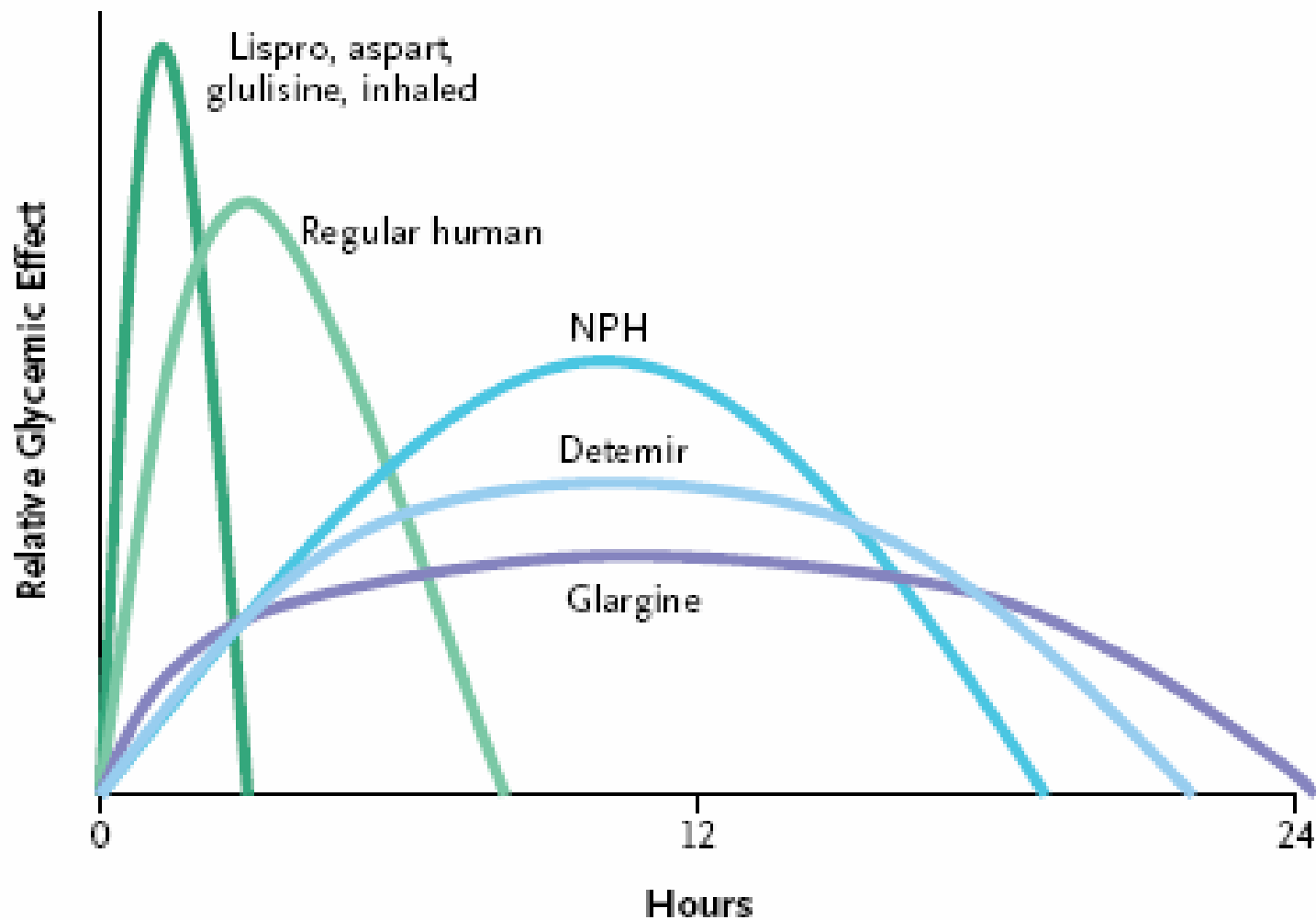
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Acute rise in glucose with a meal will trigger ROS and consequently, release of inflammatory biomarkers.

Acute control of the post-prandial glucose rise with pre-prandial insulin will inhibit the rise in inflammatory biomarkers.

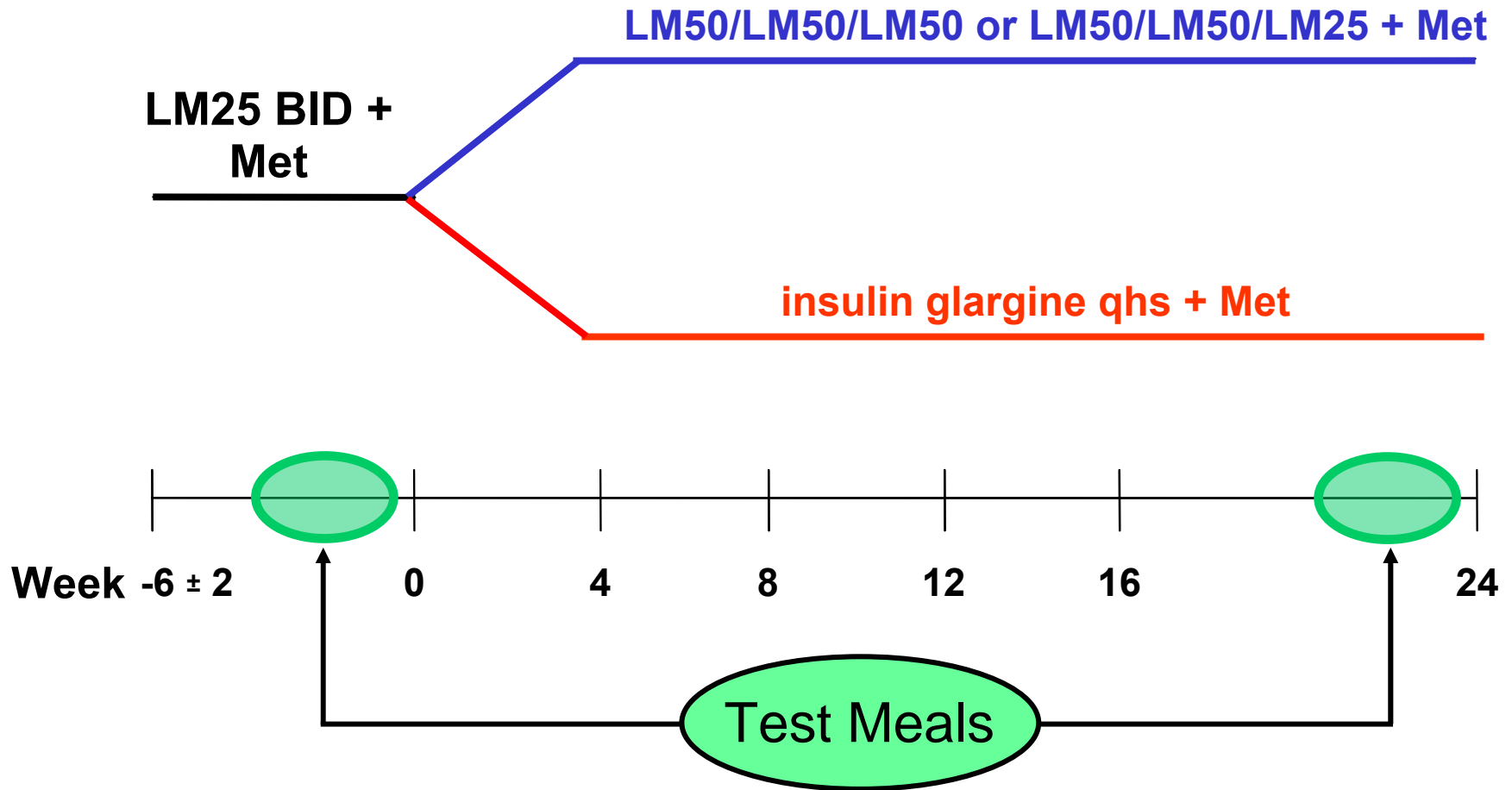
Acute rise in insulin will alter chylomicron remnant clearance.

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**Figure 1.** Schematic Time–Activity Curves for Available Insulin Formulations. Biphasic insulin preparations (not shown) combine short-acting insulin with neutral protamine Hagedorn (NPH) insulin.

# Study Design



# Endpoints

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- C reactive protein (hsCrp)
  - Tumor necrosis factor alpha (TNF $\alpha$ )
  - Interleukin six (IL-6)
  - Nitrotyrosine (NT)
  - Methylglyoxal (mG)
  - 3-Deoxyglucose (3-DG)
  - Asymmetrical dimethylarginine (ADMA)
  - Coagulation factor VII (Factor VII)
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# Endpoints

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- Each measure was compared in the Test Meal 1 to Test Meal 2 in each treatment group –
  - **Lispro-mix vs Glargine**
  - AT each point in time ) to (4 -8 hrs)
  - With the area under the curve
  - With the area under the curve adjusted for baseline (0 time) in the post prandial period.
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# Test Meal Substudy Results

## Baseline Characteristics

	Overall N=46*
Age (yr)	57.1 ± 7.5
Gender, Male [n(%)]	30 (65.2)
Ethnicity** [%]	54/17/2/4/22
Weight (kg)	98.8 ± 23.4
BMI (kg/m <sup>2</sup> )	33.7 ± 7.4
Duration of T2D (yr)	12.2 ± 6.4

Data presented mean ± sd unless otherwise stated.

\*All p-values comparing LM50+Met (n=25) vs G+Met (n=21) were non-significant

\*\*Caucasian / Black/African Descent / East or Southeast Asian / West Asian / Hispanic

# Baseline Characteristics

	LM50+Met* (n=25)	G+Met* (n=21)
Age (yr)	55.0 ± 8.0	57.9 ± 7.6
Gender, Male [n(%)]	17 (58.6)	18 (66.7)
Ethnicity** [%]	48/17/0/7/28	56/22/4/0/19
Weight (kg)	103.1 ± 24.1	96.5 ± 20.1
BMI (kg/m <sup>2</sup> )	35.6 ± 7.4	33.0 ± 6.9
Duration of T2D (yr)	11.3 ± 6.7	12.0 ± 7.1

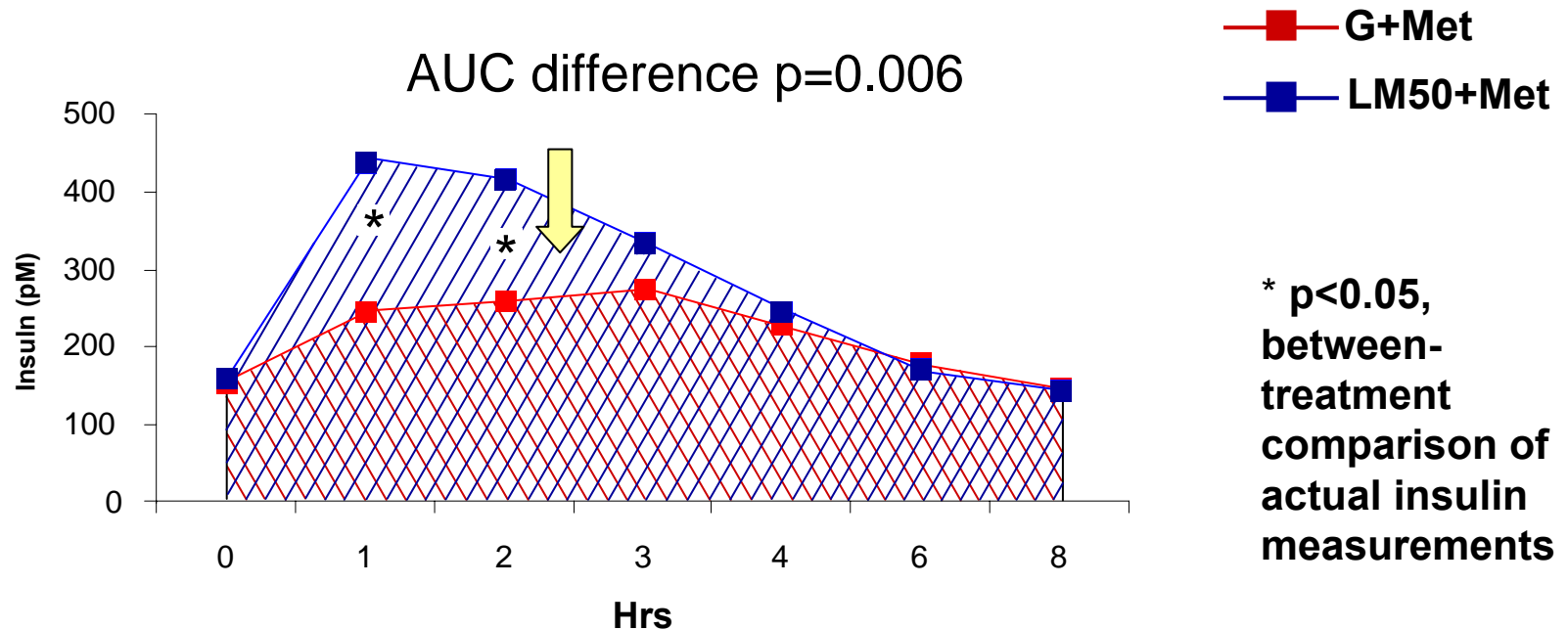
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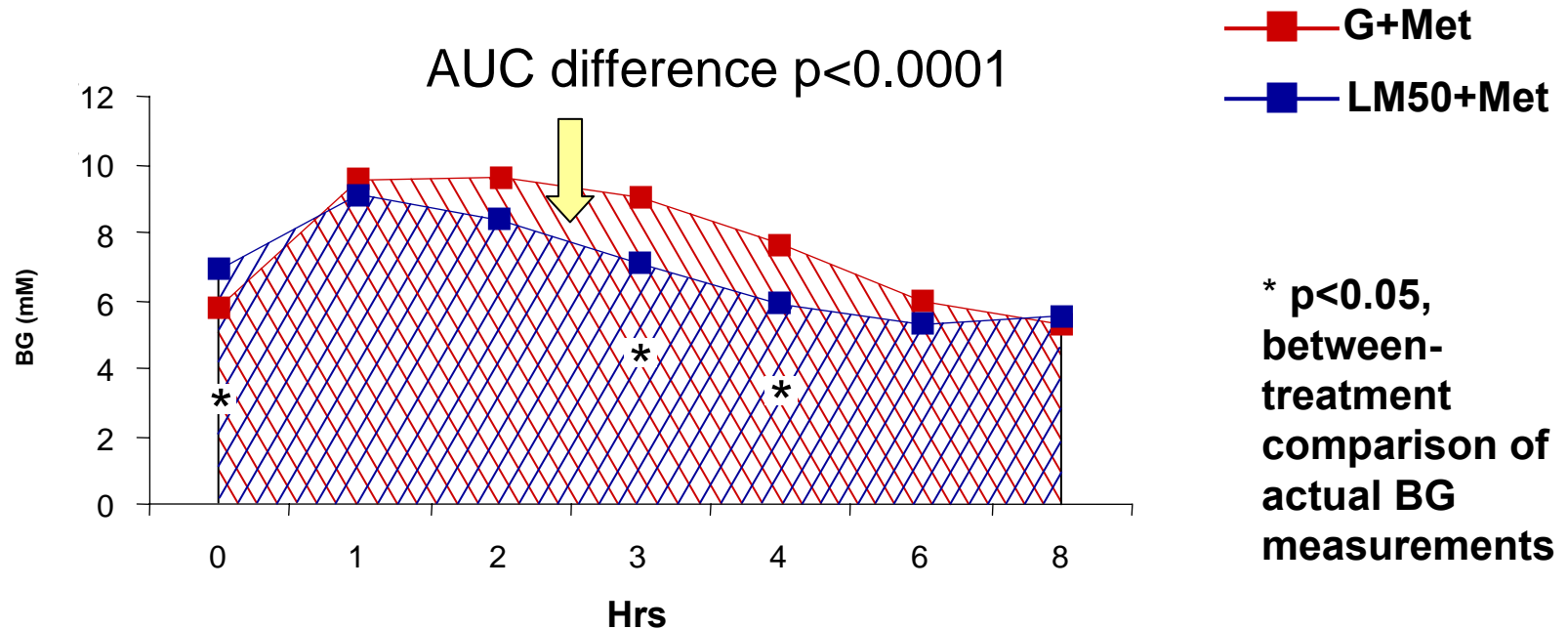
# Test Meal 2: Insulin

- AUC (0-8 hr) of insulin was higher for the LM50+Met vs G+Met group
- Insulin was higher at 1<sup>st</sup> and 2<sup>nd</sup> hr for the LM50+Met vs G+Met group



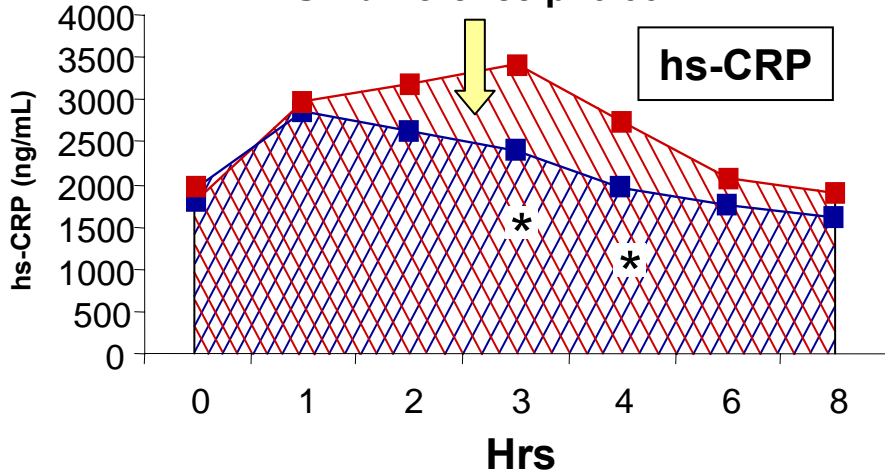
# Test Meal 2: Blood Glucose

- AUC (0-8 hr) of BG was lower for the LM50+Met vs G+Met group
- BG was lower at 3<sup>rd</sup> and 4<sup>th</sup> hr for the LM50+Met vs G+Met group, with higher BG at 0 hr for LM50+Met

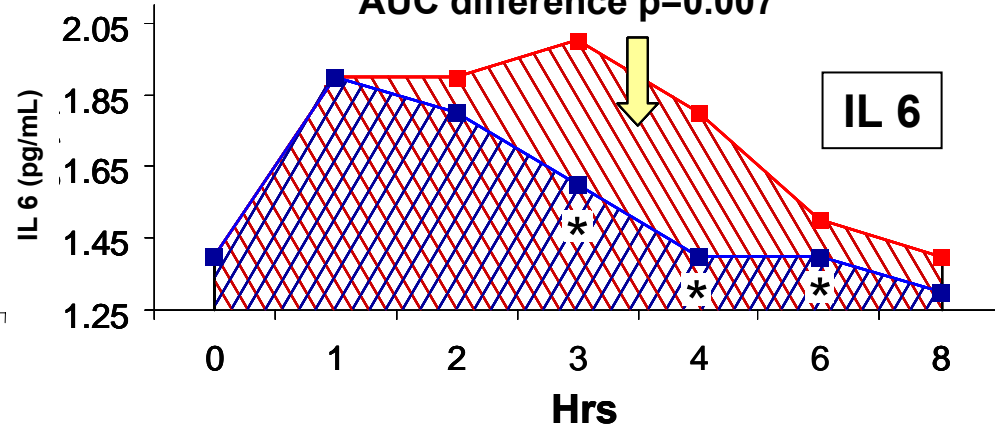


# Test Meal 2: Inflammatory Biomarkers

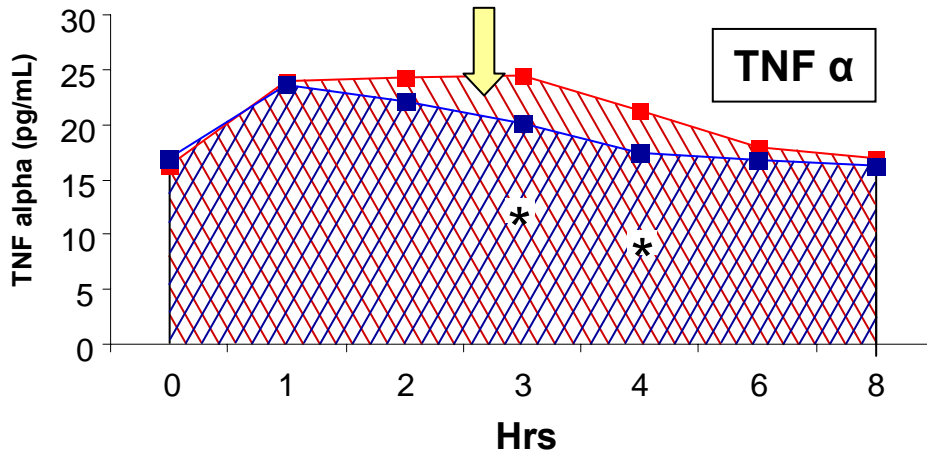
AUC difference p=0.002



AUC difference p=0.007



AUC difference p=0.005



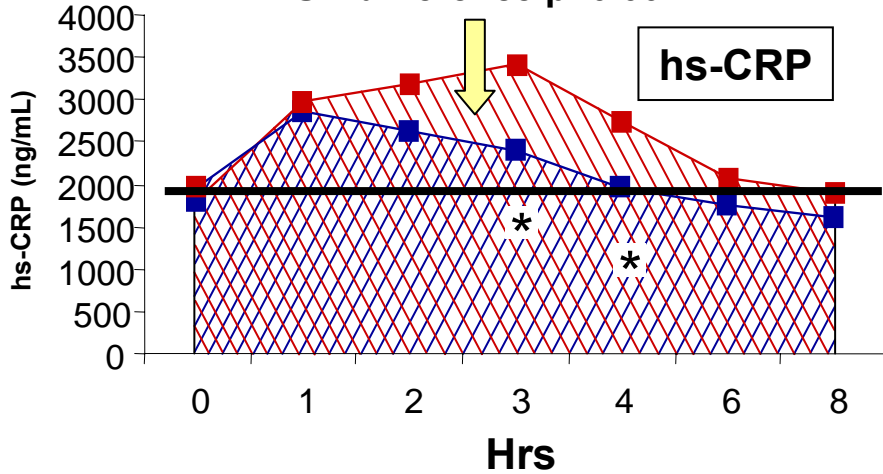
■ G+Met  
■ LM50+Met

POINT by POINT comparison

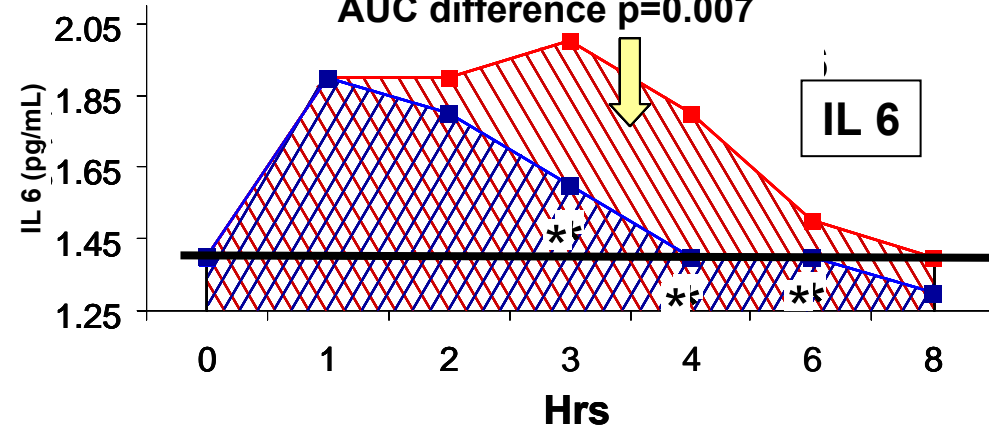
- p<0.05, between-treatment comparison of actual measurements.
- Area under the curve (AUC) comparison

# Test Meal 2: Inflammatory Biomarkers

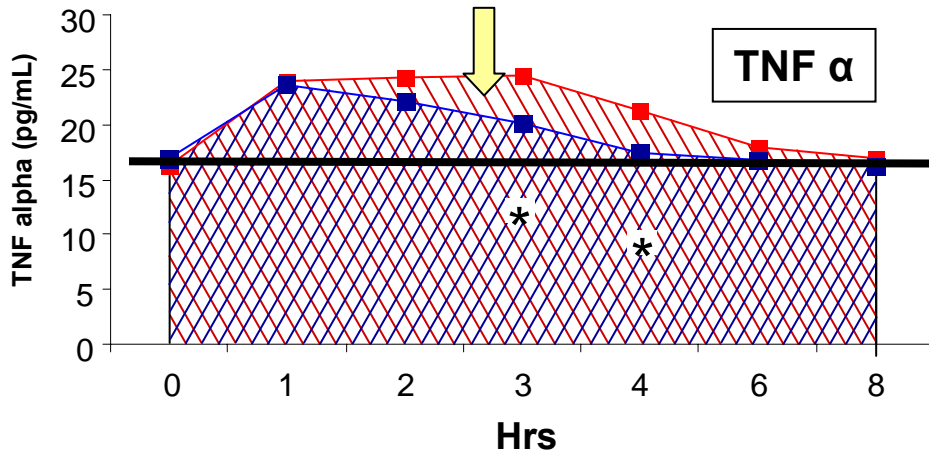
AUC difference p=0.002



AUC difference p=0.007



AUC difference p=0.005



■ G+Met  
■ LM50+Met

• Baseline adjusted AUC comparison

# Postprandial BG (0-8 hrs): Test Meal 2

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AUC:	pp BG AUC R <sup>2</sup>	P-value
pp hs-CRP	0.54	<0.001
pp TNF $\alpha$	0.30	0.02
pp IL 6	0.57	<0.001
pp NT	0.48	<0.001
AUC excursion	Pp BG AUC Excursion R <sup>2</sup>	P-value
pp hs-CRP	0.63	<0.001
pp TNF $\alpha$	0.41	0.009
pp IL 6	0.31	0.003
pp NT	0.43	<0.001

# Postprandial Insulin (0-8 hrs)

AUC:	pp INS AUC R <sup>2</sup>	pp INS AUC P-value
pp hs-CRP	0.23	0.06
pp TNF $\alpha$	0.10	0.29
pp IL 6	0.18	0.14
pp NT	0.13	0.28
AUC Excursion:	pp INS AUC Excursion R <sup>2</sup>	pp INS AUC Excursion P-value
pp hs-CRP	0.27	0.01
pp TNF $\alpha$	0.23	0.02
pp IL 6	0.18	0.14
pp NT	0.21	0.02

# Endpoints

(Area Under the Curve)

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- C reactive protein (hsCrp)
  - Tumor necrosis factor alpha (TNF $\alpha$ )
  - Interleuken six (IL-6)
  - Nitrotyrosine (NT)
  - Methylglyoxal (mG)
  - 3-Deoxyglucose (3-DG)
  - Asymmetrical dimethylarginine (ADMA)
  - Coagulation factor VII (Factor VII)
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# Changes in Lipoproteins

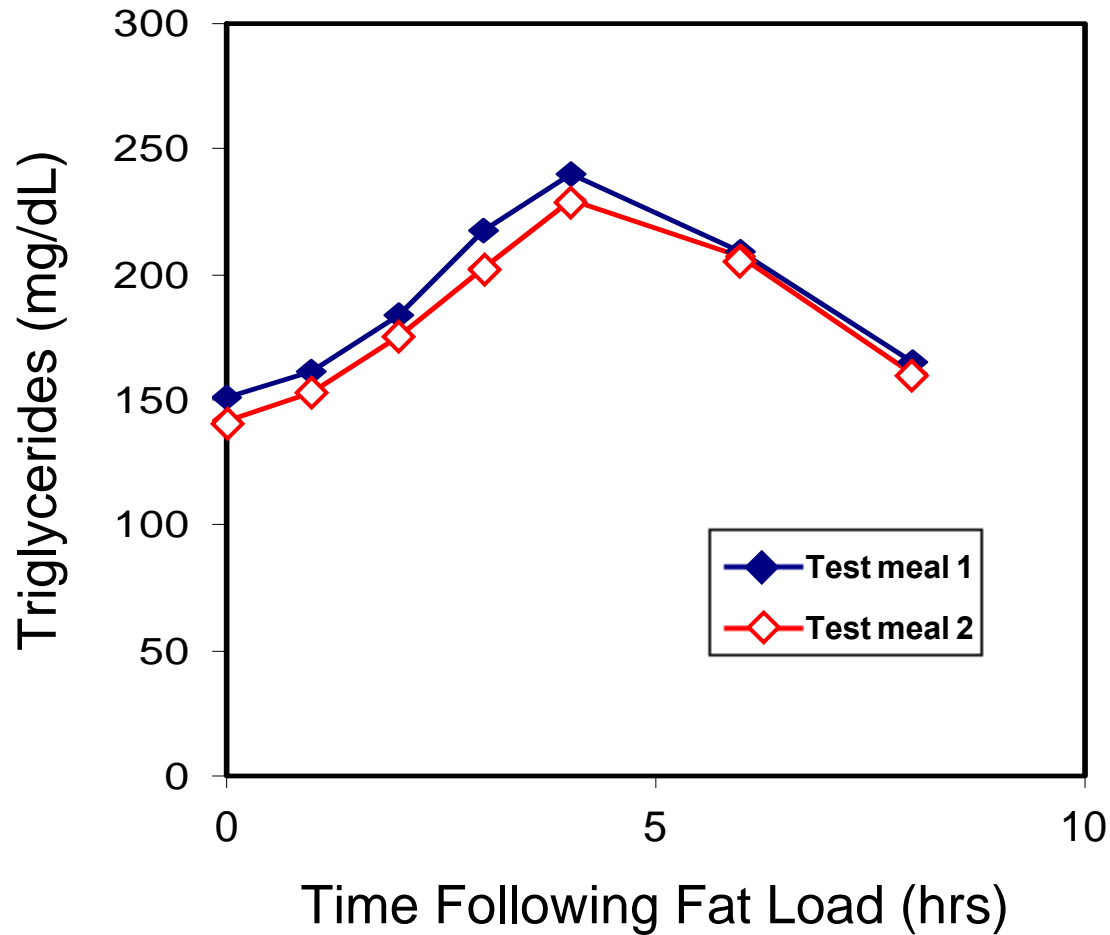
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- Lipids and Lipoproteins were measured at each time point.
  - Chylomicrons and VLDL were separated and analysed at each measure
  - Vitamin A was given as an assessment of Chlomicron remnant clearance
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# Insulin Lispro Mix50: Test Meal 1 & 2

## Plasma Triglycerides

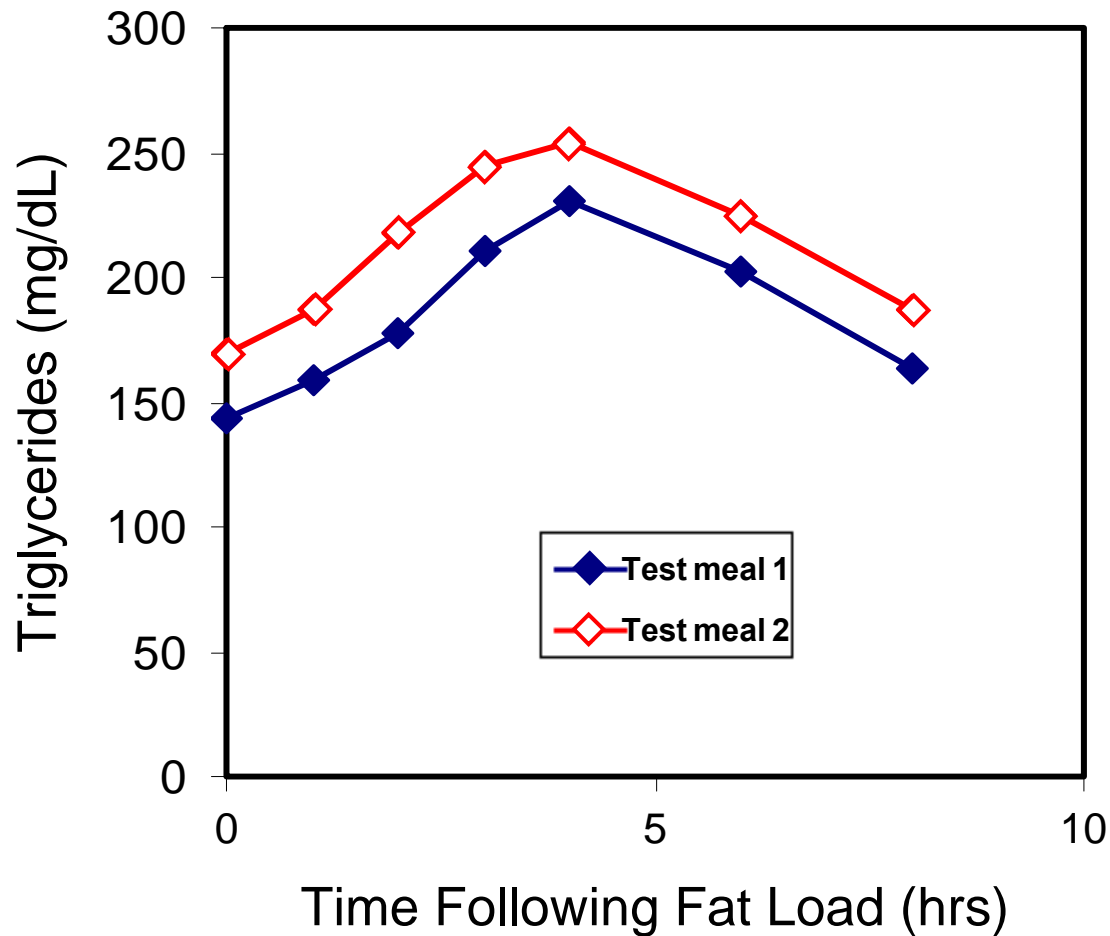
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# Insulin Glargine: Test Meal 1 & 2

## Plasma Triglycerides

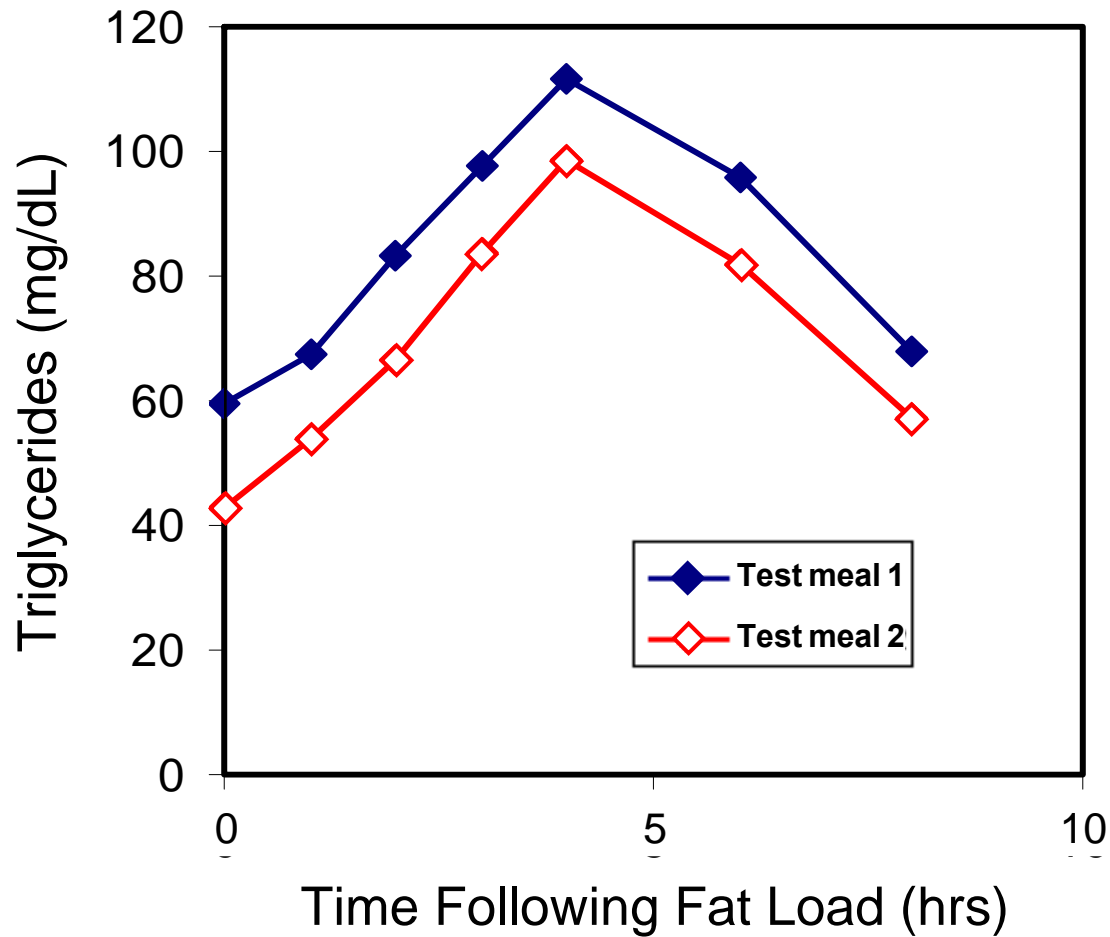
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# Insulin Lispro Mix 50: Test Meal 1 & 2

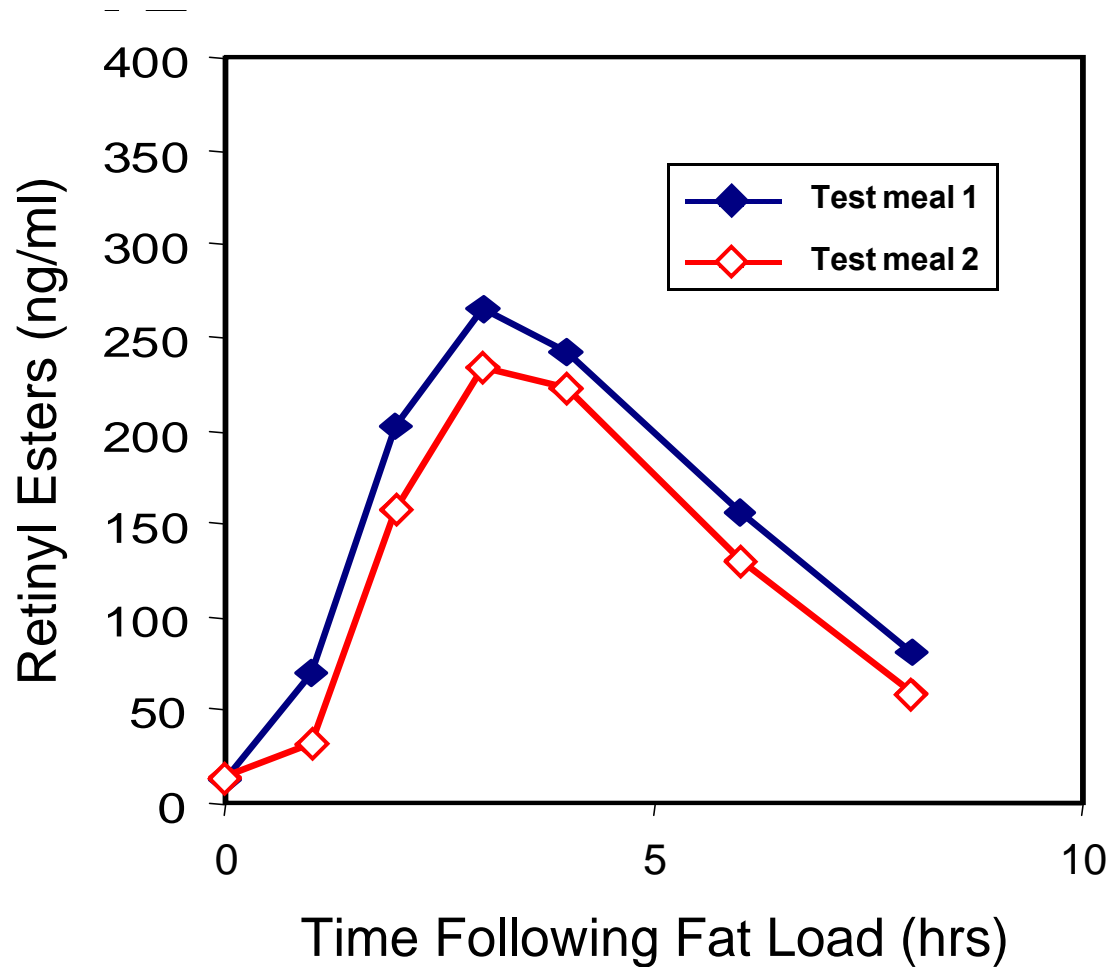
## Chylomicrons TG

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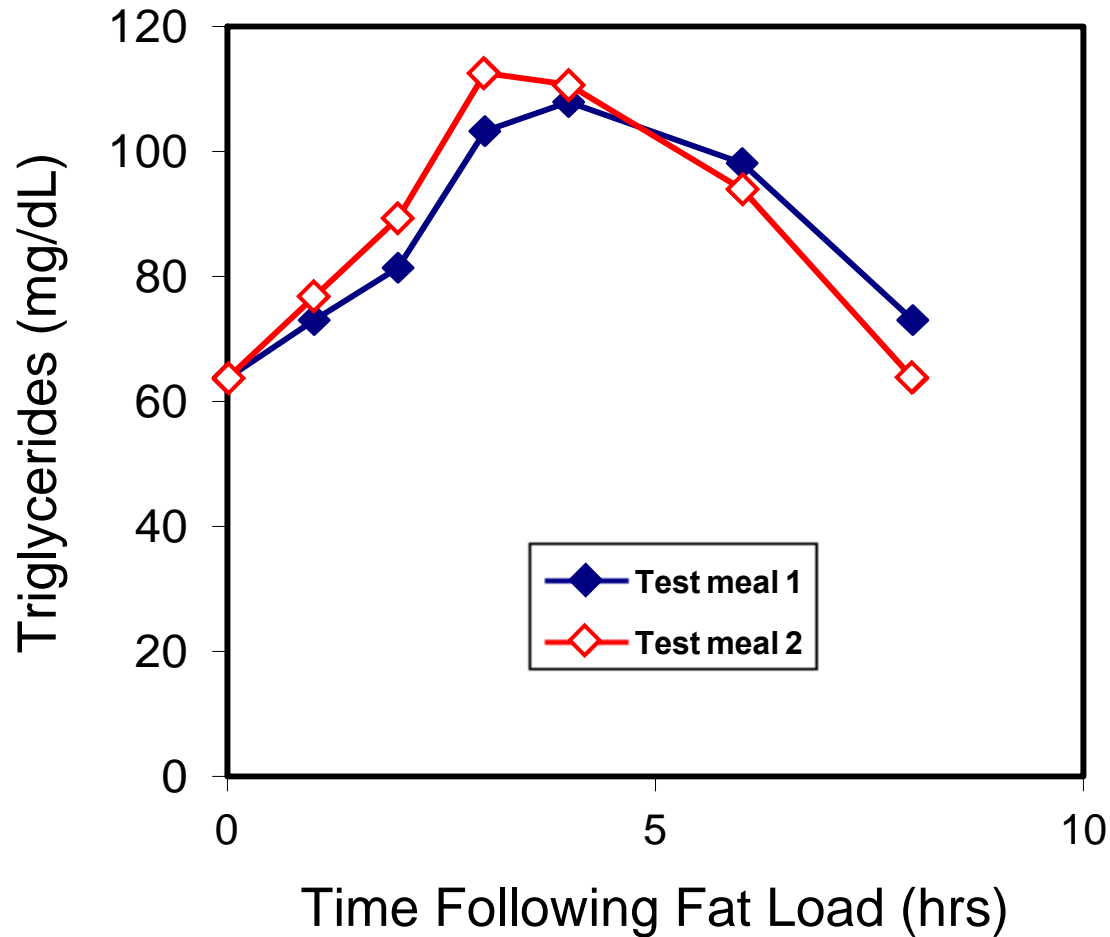
# Insulin Lispro Mix 50: Test Meal 1 & 2

## Chylomicrons RE



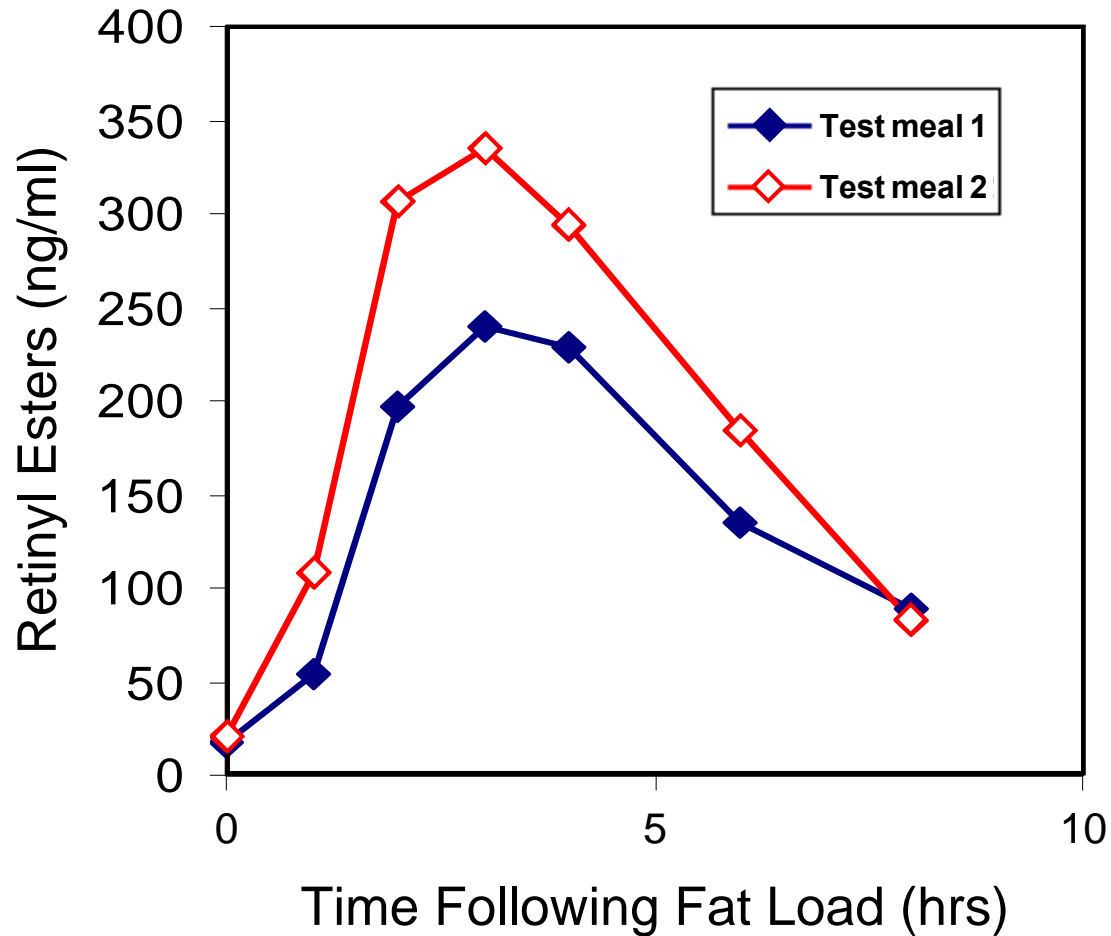
# Insulin Glargine: Test Meal 1 & 2

## Chylomicrons TG



# Insulin Glargine: Test Meal 1 & 2

## Chylomicrons RE



# Summary

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In Type 2 Diabetes mellitus preprandial insulin produces more rapid clearance of chylomicron remnants.

A series of inflammatory markers are dramatically increased in the post-prandial state. The change in concentration is

1. Reduction in the
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# Lipid Fractions: Incremental Area Under the Curve (IAUC), (corrected for 0-hr)

IAUC	LM25+Met Test meal 1	LM50+Met Test meal 2	P-value
P-TG (mg-hr/dL)	430	431	ns
Chylo-TG (mg-hr/dL)	278	321	ns
Remn-TG (mg-hr/dL)	51	36	ns
Plasma-RE (AU-hr/ml)	1312	1112	ns
Chylo-RE (AU-hr/ml)	1097	917	ns
Remn-RE (AU-hr/ml)	380	430	ns

## LM25+Met → LM50+Met

- No change in postprandial plasma TG
- Reduction in fasting chylomicron TG
- No change in postprandial chylomicron TG pattern
- No change in fasting chylomicron RE
- Trend in reduction in postprandial chylomicron RE
- No change in postprandial plasma RE

# Lipid Fractions: Incremental Area Under the Curve (IAUC), (corrected for 0-hr)

IAUC	LM25+Met Test meal 1	G + Met Test meal 2	P-value
P-TG (mg-hr/dL)	369	481	ns
Chylo-TG (mg-hr/dL)	213	306	ns
Remn-TG (mg-hr/dL)	40	80	ns
Plasma-RE (AU-hr/ml)	1427	1451	0.05
Chylo-RE (AU-hr/ml)	1051	1442	0.03
Remn-RE (AU-hr/ml)	306	474	0.005

## LM25+Met → G+Met

- Increase in peak postprandial plasma TG
- No change in fasting chylomicron TG
- No change in fasting chylomicron RE
- Increase in postprandial chylomicron RE
- Increase in postprandial plasma RE