Novel aspects of diet modulating postprandial lipaemia in cardiometabolic diseases

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Summary

1. Posprandial lipemia and cardiometabolic disease: MetS, type 2 diabetes, obesity

2. How can we modify a loss of phenotypic flexibility by diet?

3. Importance of the assessment of OFTT and OGTT in the clinical practice
POSTPRANDIAL LIPEMIA

Atherogenesis: A Postprandial Phenomenon

CIRCULATION DONALD B. ZILVERSMIT, PH.D.

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Phenotypic flexibility is a key feature of optimal health. Physiological processes involved in phenotypic flexibility:

- Kidney: (Re)absorption, Urea cycle
- Adipose tissue: Lipolysis & lipotoxicity, Adipose insulin sensitivity, Expandability, Lipokine & adipokine production, Macrophage infiltration
- Vasculature: Blood pressure regulation, Endothelial integrity & flexibility
- Gut: Host-microbe interaction, Absorption, Intestinal integrity, barrier function, Gut hormone production, Gut-mediated inflammation control, Chylomicron production
- Brain: Endocrine responses, Secondary messengers, HPA axis, Neurotransmitters & precursors
- Pancreas: β-cell function, α-cell function
- Liver: Core metabolism, Lipoprotein metabolism, Bile production, Hepatic tissue injury control, Fibrosis & inflammation, Hepatic insulin sensitivity
- Muscle: Protein metabolism, Muscle tissue injury control, Muscle insulin sensitivity

**Optimal metabolic health**

mechanisms and processes that maintain this flexibility in an organism as a phenotype.

The postprandial state

The energy pulse and the control mechanisms

- Oxidative stress
- Inflammatory stress

Decreased flexibility
- linked to ‘metabolic syndrome’
- may result in damage
Given the assumption that phenotypic flexibility is a key feature of optimal health ...

Can we quantify phenotypic flexibility?

- Fasting is not enough

Dynamic tests are needed to explore the capacity to maintain homeostasis.
Metabolic syndrome as a typical pathological condition characterized by a loss of phenotypic flexibility

**Relation between pathogenic adipose tissue and the lipid pattern: postprandial disease**

MetS have an approximate 5-fold higher risk of developing diabetes, a roughly 2-fold higher risk of developing coronary artery disease, and a high likelihood of having nonalcoholic fatty liver disorder.
Abnormal postprandial response as a surrogate marker of the “metabolic disease”

1. MetS
2. Obesity phenotypes
3. Prediabetes
The CORDIOPREV study will explore the ability of the Mediterranean diet to reduce the progression of CHD, comparing its results with the low-fat model, in a long-term (7 years) intervention study.

Figure 1. Flow-chart of CORDIOPREV study. Before participants were enrolled in the two different dietary models from CORDIOPREV study, they received an oral fat tolerance test using a weight-adjusted meal (0.7 g fat and 5 mg cholesterol per kg body weight) with 12% saturated fatty acids (SFA), 10% polyunsaturated fatty acids (PUFA), 43% monounsaturated fatty acids (MUFA), 10% protein and 25% carbohydrates (CHO).

doi:10.1371/journal.pone.0096297.g001

Rationale, methods and baseline characteristics. Am Heart J. 2016 in press.
MetS influences the postprandial response of lipids

We found a positive association between the number of metabolic syndrome criteria and the response of postprandial plasma triglycerides (p<0.001), AUC TGs (p<0.001) and incremental AUC TGs (p<0.001).

Postprandial AUC of triglycerides in relation to Mets traits. The magnitude of the AUC of postprandial TG increased in the sequence 0, 1, 2 criteria 3 criteria, 4 criteria, 5 criteria.
There is an intriguing debate over whether or not MHO and metabolically unhealthy status with normal-weight individuals have an increased risk of metabolic complications.

**Cardiometabolic abnormalities**
Cardiometabolic abnormalities were considered according to body size phenotype definitions proposed by Wildman et al. [10]. For homoeostasis model assessment of insulin resistance (HOMA-IR), we used the cut-off points of insulin resistance for the Spanish population [11], and for the high-sensitivity C-reactive protein (hs-CRP) levels, we used the cut-off point suggested for use by the CDC/AHA guidelines to define high-risk levels [12]:

1. Elevated blood pressure: systolic/diastolic blood pressure $\geq 130/85$ mmHg or antihypertensive medication use;
2. Elevated triglyceride level: fasting triglyceride level $\geq 150$ mg/dL;
3. Decreased HDL-C level: HDL-C level $<40$ mg/dL in men or $<50$ mg/dL in women or lipid-lowering medication use;
4. Elevated glucose level: fasting glucose level $\geq 100$ mg/dL or antidiabetic medication use;
5. Insulin resistance: HOMA-IR $>2.6$;
6. Systemic inflammation: hs-CRP level $\geq 3$ mg/L.
Our findings showed that certain types of the metabolic phenotypes of obesity are more favourable modulating phenotypic flexibility after a dynamic fat load test, through TG metabolism.
Patients with prediabetic showed a lower degree of flexibility by an exaggerated lipoprotein postprandial response, compared with those non-diabetic patients.

The frequency of undesirable response increases progressively according to non-diabetic (35%), patients with prediabetes (48%) and patients with diabetes (59%).
Hepatic insulin resistance both in patients with prediabetes and diabetes determines postprandial lipoprotein metabolism: from the CORDIOPREV study

It is important to understand whether the underlying causes of metabolic inflexibility may influence the maintenance of overall triglycerides homoeostasis in the prediabetic status.

The postprandial response was higher in patients with liver-IR compared with muscle-IR or without any type of IR. Finally, our results indicate an association between hepatic IR and postprandial-TG response.
Can we modify a loss of phenotypic flexibility in the Metabolic syndrome by diet?

1. Postprandial lipoprotein response.
2. Inflammation
3. Oxidative response.
4. Postprandial vascular function.
5. Proteoma
LIPGENE study
“Diet, genomics and the metabolic syndrome: an integrated nutrition, agro-food, social and economic analysis”

411 MetS patients

- n=97 HSFA (12 weeks)
- n=111 HMUFA (12 weeks)
- n=104 LFHCC + placebo (12 weeks)
- n=99 LFHCC + 1.24 g n-3 (12 weeks)

Challenge test with different type of fat

Oral Fat Tolerance Test

Niveles Basales

Horas a lo largo del día

TG
Insulina
Glucosa
Clustering of risk factors incorporated into the MetS

Includes risk factors not routinely measured

- Insulin resistance
- Small dense LDL
- Endothelial dysfunction
- Abnormal sympathetic nervous activity
- Prothrombotic markers
- Proinflammatory markers
- Oxidative stress
- Disbiosis (gut microbiota)
- Abnormal postprandial lipoprotein metabolism
Insulin resistance determines a differential flexibility to changes in dietary fat modification on MetS risk factors: the LIPGENE study

MetS HOMA-IR < 1.90

MetS HOMA-IR 1.90-2.93

MetS HOMA-IR > 2.93

Low to medium HOMA-IR exhibited reduced blood pressure, TGs, and LDL-c levels after LFHCC n-3 diet and increased apo A-I after the HMUFA and HSFA diets.

Improved IR, with reduced insulin and HOMA-IR concentrations after consumption of the HMUFA and LFHCC n-3 diets.

Clustering of risk factors incorporated into the MetS

Includes risk factors not routinely measured

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Dietary fat differentially influences regulatory endothelial function during the postprandial state in patients with MetS: LIPGENE study


We demonstrated a higher bioavailability of nitric oxide (NO) synthase after the HMUFA diet, the most potent endogenous vasodilator. NO inhibits platelet aggregation, smooth muscle cell proliferation and adhesion of monocytes to endothelial cells.

Postprandial sICAM-1 levels were lower during the HMUFA than HSFA and LFHCC n-3 diets. We can modify a loss of phenotypic flexibility by the quality of the diet.
Clustering of risk factors incorporated into the MetS

Includes risk factors not routinely measured

- Insulin resistance
- Small dense LDL
- Endothelial dysfunction
- Abnormal sympathetic nervous activity
- Prothrombotic markers
- Proinflammatory markers
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NF-κB is a pleiotropic transcription factor that regulates the expression of several cytokines, chemokines, cell adhesion molecules, immunoreceptors and inflammatory enzymes [TNFα, matrix metalloproteinases 2 (MMP-2), matrix metalloproteinases 9 (MMP-9) and tissue factor (TF)], that are involved in low-grade chronic inflammatory state.
The chronic intake of a Mediterranean diet enriched in virgin olive oil, decreases nuclear transcription factor kappaB activation in peripheral blood mononuclear cells.

![Graph showing plasma concentrations of sICAM-1 and VCAM-1](image)

**FIGURE 3.** Mean (±SEM) plasma concentrations of soluble intracellular adhesion molecule 1 (sICAM-1) at 0 and 9 h of fat intake from 3 meals (butter, olive oil, walnuts).

**FIGURE 2.** Plasma concentrations of VCAM-1 after the intake of the three dietary models. Results are means of all volunteers (n=16) ±S.E.M. *p < 0.05 vs. Western diet.

The HMUFA diet significantly reduced postprandial nuclear transcription factor-kappaB (NF-kB) activity and the nuclear p65 protein levels relative to fasting values (p < 0.05). Postprandial plasma levels of MCP-1 (not shown) were reduced after intake of HMUFA and LFHCC n-3 diets.
Our results indicate that the long-term consumption of a HMUFA attenuates the postprandial inflammatory state associated with MetS.

The expression of MMP-9 in atherosclerotic plaques coincides with the production of free radicals, which are found in greater quantity in MetS patients.

Postprandial tumor necrosis factor-α and Metalloproteinase 9 mRNA levels were also reduced after the HMUFA diet compared with the HSFA diet (p < 0.05).

Clustered risk factors incorporated into the MetS

Includes risk factors not routinely measured

- Insulin resistance
- Small dense LDL
- Endothelial dysfunction
- Abnormal sympathetic nervous activity
- Prothrombotic markers
- Proinflammatory markers
- Oxidative stress
- Disbiosis (gut microbiota)
- Abnormal postprandial lipoprotein metabolism
Postprandial response of remnant TRL (small TRL)

* P<0.05 MUFA vs. WALNUT and BUTTER

Consumption of diets with different type of fat influences triacylglycerols-rich lipoproteins particle number and size during the postprandial state

Short-term intake of the MedDiet and the acute intake of an olive oil meal lead to the formation of a reduced number and higher-size TRL particles compared with other fat. Nuclear Magnetic Resonance spectroscopy

Beneficial long-term effects of a low-fat, high complex carbohydrate diet supplemented with long-chain n-3 PUFA on postprandial lipoprotein metabolism in patients with MetS

The adverse TG raising effects of the long-term LFHCC diets may be avoided by concomitant LC n-3 PUFA supplementation to weight-stable MetS subjects.

Long-term consumption of a Mediterranean diet improves postprandial lipemia in patients with type 2 diabetes mellitus: from the Cordioprev randomized trial.
Long-term consumption of a Mediterranean diet improves postprandial lipemia in patients with type 2 diabetes mellitus: from the Cordioprev randomized trial.

Patients with T2D

**TG AUC**

<table>
<thead>
<tr>
<th>Diet</th>
<th>Baseline</th>
<th>3 Years of Follow-up</th>
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</thead>
<tbody>
<tr>
<td>LF diet</td>
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<tr>
<td>MedDiet</td>
<td><img src="image1" alt="Graph" /></td>
<td><img src="image2" alt="Graph" /></td>
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</tbody>
</table>

- TG AUC at baseline
- TG AUC at 3 years of follow-up

Patients with T2D

**RC AUC**

<table>
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<tr>
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</thead>
<tbody>
<tr>
<td>LF diet</td>
<td><img src="image3" alt="Graph" /></td>
<td><img src="image4" alt="Graph" /></td>
</tr>
<tr>
<td>MedDiet</td>
<td><img src="image5" alt="Graph" /></td>
<td><img src="image6" alt="Graph" /></td>
</tr>
</tbody>
</table>

- RC AUC at baseline
- RC AUC at 3 years of follow-up

*Significant difference
Postprandial changes in the proteome are modulated by dietary fat in patients with MetS: LIPGENE study

We analyzed the postprandial changes in the whole proteome of both nuclear and cytoplasmic fractions of PBMC by two-dimensional proteomics. 23 proteins were differentially expressed.

2-D PAGE of PBMN whole proteome

HSFA intake caused the postprandial increase of proteins responding to oxidative stress (HSPA1A, PDIA3 and PSME1) and DNA damage (SMC6) and procoagulant state, which reflect a higher postprandial oxidative stress as compared to intake of HMUFA and HPUFA meals.
Variability in postprandial response

- The magnitude of postprandial lipemia varies greatly between individuals.

- Multiple factors are associated to this variability including:
  - Age
  - Gender
  - Diabetes
  - Fasting triglyceride levels
  - Obesity
  - Dietary habits
  - Genetic factors
1. **Saturated fat**
   - ACC2 (AA)
   - ADIPOQ (CC) and ADIPOR1 (AA)
   - PLIN (AA)
   - Calpain-10 (GG)
   - TCF7L2 (TT)

2. **Med diet**
   - IRS-2 (GG)

3. **n-3 PUFA**
   - GCKR (CC)
   - IRS-2 (GG)
   - Phosphoenolpyruvate carboxykinase (CC)
After a fat load test, G/G subjects showed a higher TG postprandial response.

Our data suggest a differential phenotypic flexibility according to the rs1800629 genotype during the postprandial state.

Figure 2. Evolution of TG depending on the rs1800629 SNP in the TNF-alpha gene. Line plots of postprandial TG in G/G subjects (n = 408, continuous line, ◆) and G/A + A/A subjects (n = 99, discontinuous line, □). ANOVA for repeated measures. P1 = 0.025 genotype effect alone; P2 = 0.021, time effect alone; P3 = 0.584, genotype–time interaction.
Polymorphism at the TNF-alpha gene interacts with Mediterranean diet to influence triglyceride metabolism and inflammation status in metabolic syndrome patients: From the CORDIOPREV clinical trial

Is it possible to modify this loss of metabolic adaptation with a healthy dietary pattern (MedDiet)?

Specifically, the detrimental profile associated with the G/G genotype, expressed as higher TG and hsCRP plasma concentrations at baseline, improved after 1 year of dietary intervention.

The presence of rs1800629 at the TNF-alpha gene interacts with MedDiet to improve TG metabolism and inflammation status in MetS subjects.

IMPORTANCE OF THE ASSESSMENT OF THE OFTT and OGTT in the CLINICAL PRACTICE
OFTT.....first steps
Who should be tested for a postprandial hypertriglyceridaemia

Assessment and Clinical Relevance of Non-Fasting and Postprandial Triglycerides: An Expert Panel Statement

Genovefa D. Kolovou¹, Dimitri P. Mikhailidis², Jan Kovar³, Dennis Lairon⁴, Børge G. Nordestgaard⁵, Teik-Chye Ooi⁶, Pablo Perez-Martinez⁷, Helen Bilianou⁸, Katherine Anagnostopoulou¹ and George Panotopoulos⁹

Not be performed in subjects with fasting TG concentration of less than 1mmol/l (89mg/dl) because commonly do not have exaggerated and delayed response of TGs to a FTT; and not to perform in individuals with fasting TG concentration above 2 mmol/l (180mg/dl) because most of the time will have exaggerated and delayed response of TG to a FTT, and therefore will not benefit diagnostically from a FTT.

Thus, subjects with fasting TGs concentration between 1-2mmol/l (89-180 mg/dl) would benefit being tested with a OFTT.

Kolovou GD et al. Curr Vasc Pharmacol. 2011 May;9(3):258-70
Prevalence of undesirable postprandial TGs in the CORDIOPREV (A) and GOLDN (B) population according to fasting TGs: 1. TG < 89 mg/dl (< 1 mmol/l); 2. TG 89-180 mg/dl (1-2 mmol/l), and, 3. TG >180 mg/dl (> 2 mmol/l).

These 2 studies validate the predictive values reported in a previous consensus. Moreover, the findings of the CORDIOPREV and GOLDN studies may identify those subjects with fasting TG between 1-2 mmol/L (89-180 mg/dL) that should undergo a standardized OFTT.

The OFTT can identify an exaggerated postprandial response and this information may be useful for risk stratification or even treatment.

1. There are several processes and mechanisms involved in phenotypic flexibility including TG metabolic regulation, glucose regulation, optimal inflammatory balance, oxidative stress regulation, endothelial function and many others.

2. Most of these mechanisms are disrupted in MetS patients

3. Diet can be a good target for modulating a loss of phenotypic flexibility

4. Application of challenge tests into clinical practice is difficult but may be useful for risk stratification or even treatment
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