Ectopic fat concept and cardiovascular risk

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Declaration of interest

- Associate Editor of *Angiology*

- Associate Editor of *Clinical Lipidology*

- Associate Editor of the *Hellenic College of Treatment of Atherosclerosis* for *The Open Cardiovascular Medicine Journal*

- Section Editor of *Archives of Medical Science*

- Book Review and News and Views Editor of *Current Vascular Pharmacology*

- Editorial Board Member of *Metabolism Clinical and Experimental* and *Current Medical Research and Opinion*
Declaration of interest

- NK has given talks, attended conferences and participated in trials sponsored by Amgen, Angelini, Astra-Zeneca, Boehringer Ingelheim, Galenica, MSD, Novartis, Novo Nordisk, Sanofi and WinMedica
FAT-ADIPOSE TISSUE
Subcutaneous vs visceral adipose tissue
Systemic and local effects of “ectopic” fat deposition

INTRAHEPATIC FAT

NON-ALCOHOLIC FATTY LIVER DISEASE – NAFLD
NAFLD: obesity and T2DM

• NAFLD is defined by fat accumulation in ≥5% of the hepatocytes (in the absence of alcohol abuse or other causes of hepatic disease)

• NAFLD is the most common chronic liver disease worldwide, representing a hepatic manifestation of the metabolic syndrome (MetS)

• NAFLD prevalence:
  - 20-30% in the general population
  - 30-90% in obesity
  - 60-70% in T2DM
NAFLD and CVD risk

- Prevalence and severity of CHD, stroke and PAD
- Coronary and aortic calcification
- Subclinical atherosclerosis (i.e. FMD, cIMT, arterial stiffness)
- Epicardial fat thickness
- CKD
- Obstructive Sleep Apnoea (OSA)
- Erectile Dysfunction (ED)
- Hyperuricemia
- Rheumatic Diseases (i.e. RA, SLE, psoriasis)
NAFLD is an independent risk factor for cardiovascular disease

• NAFLD is associated with several established and emerging CVD risk factors

• NAFLD is associated with increased CVD prevalence

• The majority of deaths among NAFLD patients are attributed to CVD

• NAFLD, T2DM and CVD share common pathogenic mechanisms and multiple molecular mediators
Coronary Heart Disease Risk and NAFLD

Systematic Review and Meta-Analysis

4 cross-sectional studies and 2 prospective cohort studies = 7,042 participants.

Pooled effects estimate: NAFLD is a predictor of cardiovascular disease independent of conventional risk factors (OR 1.50, 95% CI, 1.21 to 1.87; p < 0.001).

Lu H, et al. *Int J Endocrinol* 2013; 124958
Should we expand the concept of coronary heart disease equivalents?

Niki Katsiki, Vasilios G. Athyros, Asterios Karagiannis, Anthony S. Wierzbicki, and Dimitri P. Mikhailidis

Purpose of review
This narrative review discusses the associations between metabolic and inflammatory diseases, as well as radiotherapy and chemotherapy with coronary heart disease (CHD) and related risk factors, to support (or not) their potential role as CHD equivalents.

Recent findings
Although not regarded as CHD equivalents, several metabolic and inflammatory disorders are associated with an increased risk of CHD morbidity and/or mortality. These conditions include metabolic syndrome, impaired glucose metabolism, nonalcoholic fatty liver disease, obstructive sleep apnoea syndrome, erectile dysfunction, periodontitis, inflammatory bowel diseases, systemic vasculitis and HIV infection, as well as chemotherapy and radiotherapy.

Summary
More research should be carried out to identify which conditions can be added to the list of CHD equivalents.

Keywords
coronary heart disease equivalent, erectile dysfunction, metabolic syndrome, nonalcoholic fatty liver disease, obstructive sleep apnoea syndrome
Should we expand the concept of coronary heart disease equivalents?

**KEY POINTS**

- Noncardiac vascular diseases (carotid artery disease, PAD and AAA), diabetes and CKD are regarded as CHD equivalents.

- MetS, IFG, IGT, NAFLD, OSA syndrome, erectile dysfunction, periodontitis, IBDs, systemic vasculitis and HIV infection are associated with increased risk for CHD morbidity and/or mortality. Radiotherapy and chemotherapy may also raise CHD risk.

- MetS and NASH share common pathogenetic mechanisms, risk factors and therapeutic strategies with CHD, thus supporting their role as CHD equivalents. Nevertheless, such recognitions remain to be established in future guidelines.

- Physicians should be aware of these associations in order to identify those at high risk who will benefit from appropriate treatment to reduce CHD risk.

Katsiki N et al. Curr Opin Cardiol 2014; 29: 389 - 95
EASL–EASD–EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease☆

European Association for the Study of the Liver (EASL)*, European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity (EASO)

Recommendations

- In persons with NAFLD, screening for diabetes is mandatory, by fasting or random blood glucose or HbA1c (A1) and if available by the standardized 75 g OGTT in high-risk groups (B1)

- In patients with T2DM, the presence of NAFLD should be looked for irrespective of liver enzyme levels, since T2DM patients are at high risk of disease progression (A2)
NAFLD develops from simple steatosis to steatohepatitis (NASH), and then cirrhosis. Cirrhosis is no more reversible.
Treatment options for NAFLD

**Lifestyle** (Mediterranean diet, exercise)

**Risk factors** (BP, lipids, glycaemia, smoking)

**Potential drugs** (pioglitazone, antihypertensive drugs, statins, vitamin E, orlistat, ezetimibe, ursodeoxycholic acid and several glucose lowering drugs)

**Bariatric surgery**

There is a need for more research!!!!
Multifactor-based study

- 54 weeks; MetS n = 186
- Biochemical and ultrasound evidence of NAFLD

- **Atorvastatin**: 67% no longer had “NAFLD”
- **Fenofibrate**: 42% no longer had “NAFLD”
- **Combination**: 70% no longer had “NAFLD”

GREACE Study: NAFLD and Statins

- CHD + NAFLD: more events than CHD without NAFLD group
- CHD + NAFLD more benefit from statin treatment than CHD without NAFLD (68 vs 39%; p = 0.007)
- Statin use “safe” in NAFLD patients with CHD

Limitations: post-hoc, small n, NAFLD Diagnosis

ATTEMPT Study

• 326 participants, had modestly elevated LFTs and ultrasonographic evidence of NAFLD (165 in group A2; 161 in group B2).

• NAFLD resolved during the 42-month treatment period in 86% of patients in group A2 and in 74% of patients in group B2 (p < 0.001). In both groups nearly 90% of patients attained lipid goals.

• As expected, LDL-C and TG levels were higher in group B2 than in group A2 (p < 0.001).

• There were no CVD events in group A2 whereas 5 non-fatal events occurred in group B2 (log-rank-p = 0.024).

• There were no major side-effects.

IDEAL (Incremental Decrease in Endpoints Through Aggressive Lipid Lowering) study

n = 7782 ALT below ULN and n = 1081 ALT below ULN (48 iu/l for men and 36 iu/l for women)
Simvastatin (20 – 40 mg/day) vs atorvastatin (80 mg/day). All patients post-MI; 4.8 years follow-up.

Like in GREACE, ALT activity fell in those with baseline values above the ULN. The fall was greater with more aggressive statin use. It rose (≈ 4 u/l) in those with normal ALT values.

Event reduction among those with raised ALT: event rates were lower in those on aggressive therapy (6.5 vs 11.5%; p = 0.006)

Prospective Study

Resolution of non-alcoholic steatohepatitis by rosuvastatin monotherapy in patients with metabolic syndrome

Konstantinos Kargiotis, Vasilios G Athyros, Olga Giouleme, Niki Katsiki, Evangelia Katsiki, Panagiotis Anagnostis, Chrysoula Boutari, Michael Doumas, Asterios Karagiannis, Dimitri P Mikhailidis
NASH resolution following rosuvastatin 10 mg/d monotherapy

Before

After

Kargiotis K et al. WJG 2015; 21: 7860 - 8
Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study

Liraglutide was safe, well tolerated, and led to histological resolution of non-alcoholic steatohepatitis, warranting extensive, longer-term studies.

Non-alcoholic fatty liver disease in patients with type 2 diabetes mellitus: effects of statins and antidiabetic drugs

Combination therapy with a statin + liraglutide + a sodium-glucose co-transporter 2 (SGLT2) inhibitor may represent another option to further reduce CVD-related morbidity and mortality, as well as liver-related morbidity, although more data are needed to support this therapeutic option.

The use of statins alone, or in combination with pioglitazone and other drugs, for the treatment of non-alcoholic fatty liver disease/non-alcoholic steatohepatitis and related cardiovascular risk.

An Expert Panel Statement

<table>
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<th>Study</th>
<th>Participants</th>
<th>Possible NAFLD</th>
<th>Prospective Duration</th>
<th>Statin</th>
<th>Laboratory test outcome</th>
<th>Clinical outcome</th>
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<tr>
<td>GREACE [43]</td>
<td>n = 1600</td>
<td>n = 437</td>
<td>3 years</td>
<td>Atorvastatin vs usual care</td>
<td>Normalization in liver ultrasound and liver enzymes</td>
<td>Significant reduction in CVD events</td>
</tr>
<tr>
<td>IDEAL [44]</td>
<td>n = 8864</td>
<td>n = 1081</td>
<td>5 years</td>
<td>Atorvastatin vs simvastatin</td>
<td>Normalization in liver ALT levels</td>
<td>Significant reduction in CVD events</td>
</tr>
<tr>
<td>ATTEMPT [49]</td>
<td>n = 1123</td>
<td>n = 326</td>
<td>42 months</td>
<td>Atorvastatin vs atorvastatin</td>
<td>Normalization in liver ultrasound and liver enzymes</td>
<td>Reduction in CVD events</td>
</tr>
<tr>
<td>Athyros et al. 2006 [50]</td>
<td>n = 186</td>
<td>n = 186</td>
<td>54 weeks</td>
<td>Atorvastatin, fenofibrate,</td>
<td>Normalization in liver ultrasound and liver enzymes</td>
<td>Significant reduction in evaluated CVD events</td>
</tr>
<tr>
<td>Angulo et al. 2015 [51]</td>
<td>n = 619</td>
<td>n = 63</td>
<td>12.6 years</td>
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<td>-</td>
<td>Significant reduction in mortality/liver transplantation</td>
</tr>
<tr>
<td>Rallidis et al. 2004</td>
<td>n = 5 Pilot</td>
<td>n = 5</td>
<td>6 months</td>
<td>Pravastatin</td>
<td>Improvement of inflammation of the liver</td>
<td>-</td>
</tr>
<tr>
<td>Hyogo et al. 2008 [54]</td>
<td>n = 31</td>
<td>n = 31</td>
<td>24 months</td>
<td>Atorvastatin</td>
<td>Liver enzymes and steatosis and NAFLD activity score were notably improved</td>
<td>-</td>
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<tr>
<td>Kargiotis et al. 2014 [55]</td>
<td>n = 20 Pilot</td>
<td>n = 20</td>
<td>12 months</td>
<td>Rosuvastatin</td>
<td>Complete NASH resolution, liver function tests and ultrasonogram normalized</td>
<td>-</td>
</tr>
<tr>
<td>Dongiovanni et al. 2015 [57]</td>
<td>n = 1201</td>
<td>n = 107</td>
<td>Cross-sectional</td>
<td>Various statins dose-dependent manner</td>
<td>Amelioration of NASH more pronounced in patients on statins not carrying the variant I148M</td>
<td>-</td>
</tr>
<tr>
<td>Nascimbeni et al. 2016 [60]</td>
<td>n = 346</td>
<td>n = 346</td>
<td>Cross-sectional</td>
<td>Various statins</td>
<td>Amelioration of NASH and serious liver fibrosis</td>
<td>-</td>
</tr>
</tbody>
</table>

The change of statin dose every 6 weeks and the addition of ezetimibe 6 weeks after the maximum tolerated statin dose (close monitoring: mainly ALT, AST, and CPK until the LDL-C goal is attained, <70 or <100 mg/dl according to total CVD risk).
EPICARDIAL FAT
Epicardial fat and vascular risk: a narrative review

Niki Katsiki\textsuperscript{a}, Dimitri P. Mikhailidis\textsuperscript{b}, and Anthony S. Wierzbicki\textsuperscript{c}

Purpose of review
We comment on the associations between epicardial adiposity and cardiovascular disease (CVD) and associated risk factors. The effects of lifestyle measures and CVD drugs on cardiac adipose tissue are also discussed.

Recent findings
Epicardial adipose tissue exerts cardioprotective properties; however, in cases of pathological enlargement, epicardial fat can lead to myocardial inflammation and dysfunction as well as left ventricular hypertrophy and coronary artery disease (CAD) due to paracrine actions that include increased production of reactive oxygen species, atherogenic and inflammatory cytokines. Cardiac adiposity is associated with CAD, obesity, type 2 diabetes, metabolic syndrome, nonalcoholic fatty liver disease, and chronic kidney disease, as well as with CVD risk factors such as lipids, hypertension, obesity markers, and carotid atherosclerosis.

Summary
Due to its anatomical and functional proximity to the coronary circulation, epicardial adipose tissue may represent an even more direct CVD risk marker than central adiposity. Lifestyle measures and certain drugs may affect its thickness, although there are limited data currently available. The clinical implications of epicardial fat in daily practice remain to be established in future studies.

Keywords
cardiovascular disease, drugs, epicardial fat, lifestyle measures, vascular risk factors
Epicardial adipose tissue: at the heart of the obesity complications

Valeria Guglielmi¹,² • Paolo Sbraccia¹,²

Fig. 1 Potential signaling pathways mediating the cross talk between EAT, myocardium and coronary vessels
Therapeutic options to reduce epicardial fat

- Lifestyle measures
- Bariatric surgery

- Antidiabetic drugs
  - Exenatide
  - Liraglutide
  - Sitagliptin
  - Luseogliflozin
  - Basal insulin

- Hypolipidemic drugs

Elisha B et al. Horm Metab Res 2016; 48: 42 - 7
PERIVASCULAR FAT
Perivascular adiposity and vascular dysfunction

Perivascular adiposity affects vascular homeostasis

Gil-Ortega M et al. Trends Endocrinol Metab 2015; 26: 367 - 75
Perivascular fat: inflammation and oxidative stress

- In normal-weight individuals: perivascular fat exhibits vasodilatory and anti-inflammatory properties and prevents neointimal hyperplasia
- In the presence of obesity, MetS, hypertension, diabetes and smoking: predominance of inflammatory adipokines and pro-oxidant factors
- These imbalances can lead to insulin resistance, oxidative stress and vascular dysfunction including vasoconstriction, endothelial dysfunction, as well as aneurysm and neointimal formation

Schäfer K et al. Int J Obes (Lond) 2017 May 22 [Epub ahead of print]
Therapeutic options to reduce perivascular fat

- Bariatric surgery
- Antidiabetic drugs
  - Metformin
  - Pioglitazone
- Hypolipidemic drugs
  - Statins

INTRAMUSCULAR FAT
Intramuscular adiposity

- Intramyocellular fat accumulation represents an energy source during exercise
- Increased dietary fat intake and plasma fatty acid concentrations lead to abnormal intramuscular fat storage
- In such cases, intramuscular adiposity may result in insulin resistance and metabolic disorders via impaired fatty acid and triglyceride metabolism

Therapeutic options to reduce intramuscular fat

- Bariatric surgery
- Antidiabetic drugs
  - Metformin
  - Pioglitazone

Kim MK et al J Diabetes Investig 2014; 5: 221 - 7
PERIPANCREATIC FAT
Peripancreatic adiposity

- Limited data

- Peripancreatic fat volume has been strongly related to the presence and severity of acute pancreatitis

- Pancreatic adiposity has also been associated with obesity, NAFLD and T2DM

PERIRENAL FAT
Perirenal adiposity

- Limited data
- May affect renal function
- Perirenal fat has been linked to obesity, MetS, microalbuminuria and hypertension
- Perirenal adiposity has also been associated with visceral and liver fat deposition

Abnormal Peri-organ or Intra-organ Fat (APIFat)

Abstract: Adipose tissue, a major endocrine organ, consists of brown and white adipocytes. Brown fat may play a beneficial role in cardiometabolic disorders. Brown adipose tissue can also improve glucose and lipid metabolism. In contrast, the expansion of white adipose tissue has been related to obesity, type 2 diabetes mellitus and cardiovascular disease (CVD). Both the quantity and the quality of the white adipose tissue as well as its distribution may affect CVD risk. In this context, the link between adiposity and CVD risk is greater for visceral than subcutaneous fat. Apart from these fat depots, there are other adipose tissues that are either systemically (i.e. in the liver, muscle or neck) or mainly locally acting (i.e. pericardial/epicardial, perivascular and perirenal). These fat depots can affect the nearby anatomic organs via lipid accumulation and cytokine secretion.

In the present narrative review, the associations of excessive peri-organ adipose tissue, namely intrahepatic, epicardial/pericardial, perivascular, intramuscular, peripancreatic and perirenal fat, with cardiometabolic and CVD risk factors are discussed. The effects of drugs that target vascular risk and/or different fat depots are also considered.
# Abnormal Peri-Organ or Intra-organ Fat (APIFat) Deposition: An Underestimated Predictor of Vascular Risk?

Niki Katsiki\textsuperscript{1}, Vasilios G. Athyros\textsuperscript{1} and Dimitri P. Mikhailidis\textsuperscript{2*}

| Intrahepatic fat (NAFLD) | • Coronary artery calcium score  
• High-risk coronary plaques  
• CHD  
• Microvascular dysfunction  
• CVD risk factors (obesity, dyslipidaemia, insulin resistance)  
• Metabolic syndrome  
• Arterial stiffness | Lifestyle measures  
Antihypertensive drugs  
Antiobesity drugs  
Hypoglycaemic drugs Hypolipidaemic drugs |
|-------------------------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| Epicardial and pericardial fat | • Coronary artery calcification  
• Abnormal myocardial flow reserve  
• Coronary plaque vulnerability  
• CHD presence and severity  
• CHD morbidity and mortality  
• CVD risk factors (obesity, dyslipidaemia, hypertension, smoking, insulin resistance)  
• Endothelial dysfunction  
• Carotid atherosclerosis  
• Metabolic syndrome  
• Arterial stiffness | Lifestyle changes  
Hypoglycaemic drugs  
Hypolipidaemic drugs |
| Perivascular fat | • Coronary artery calcification  
• CVD risk factors (obesity, hypertension, smoking, dyslipidaemia and impaired glucose metabolism)  
• Metabolic syndrome  
• Arterial stiffness | Bariatric surgery  
Statins |
| Intramuscular fat | • CVD risk factors (obesity, dyslipidaemia and impaired glucose metabolism)  
• Metabolic syndrome | Hypoglycaemic drugs |
| Peripancreatic fat | • Presence and severity of acute pancreatitis  
• Obesity  
• NAFLD | |
APIFat syndrome

- It is likely that excess fat in any single organ is accompanied by the same pattern in other organs.

- It follows that this relationship may account for the excessive CVD risk attributed to abnormal fat deposition in any one organ.
Prevention is better than cure...