Adipose Tissue, Inflammation, and Atherosclerosis

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Medical University of Graz, Austria
Background
Obesity a global epidemic

Also in Asia
The rate of obesity in China has increased by 97% in 10 years, according to a government report.
Obesity Sequeals

- MI
- Stroke
- Heart attack
- Hypertension
- Fatty Liver
- Overweight/Obesity
- Cancer
  - Gut, Prostate, Breast, Renal, Liver, Esophagus, Melanoma
- Inflammation
- Atherosclerosis
- Type II Diabetes
- Hypertension
- Fatty Liver
- Postoperative complications e.g. Sepsis
- Cirrhosis, HCC
  - 1975: 1.4 per 100,000
  - 2006: 3.9 per 100,000
Atherosclerosis
A major burden of obesity

„Lifestyle“
Early beginning
„fatty streaks“
increased IMT

Lifelong disease

Chronic immune mediated inflammation

0  10  20  30  40  50  60  70 yrs

Stroke
Endstage

Medical University of Graz
Obesity and Atherosclerosis
A complex interaction

Clinical endpoints

Adipokines

Immune system

SAT Distribution

Obesity

Chronic vascular inflammation
The “Obesity Paradox”

Irrespective of treatment strategy, obese have lower mortality compared to lean patients

Kaplan-Meier survival in patients with established coronary artery disease (CAD)

Despite “Obesity Paradox”
Obesity is life-threatening
• Better outcome in cases of CAD and increased Mortality in Obesity – a contradiction?

• Answers may be given by the complex function of the adipose tissue.
Adipose tissue
Inflamed in obesity

Proinflammatory adipokine-cytokine “cocktail”

modified from Tilg H., Moschen A.: Nature Review Immunology, 6:772-83, 2006
The Adipose Tissue
An Immune / Endocrine Organ

Endocrine activities of adipocytes

- Leptin*
  - Eating habits
- Plasminogen activator inhibitor (PAI-1)
  - Clotting
- Resistin, Visfatin
  - Typ II Diabetes
- Angiotensinogen
  - Blood pressure
- TNF-α
  - Inflammation
- MCP-1(CCL2)
  - Inflammation, Monocytes
- Adiponectin*
  - Vasoprotection
- IL-6
  - Inflammation

*proinflammatory

*most abundant adipokines
Adiponectin
Three subfractions

- Low Molecular Weight (LMW) Adiponectin **trimer**
- Medium Molecular Weight (MMW) Adiponectin **hexamer**
- High Molecular Weight (HMW) Adiponectin **oligomer**

Oligomerisation

Source

 globular domain

 collagenous domain

atheroprotective
Adiponectin
Effects on monocyte adherence
Immune activation in early and advanced Atherosclerosis

**Inhibition by adiponectin**

**Perpetuation**

- Influence of cytokine polymorphisms

**Vicious circle of inflammation, lipid deposition, and further inflammation**

- Fractalkin
- RANTES
- GM-CSF
- M-CSF

- CRP

**Complicated lesion**

- monocytes
  - CXC3^1^ CR1^1^ CCR2^1^ Ly6C^1^ CD14^1^ CD16^1^

**Altered immune reactivity**

- T-cells
  - Th1^1^ / Th2^1^
  - IL-12^1^
  - IL-18^1^
  - IL-10^1^

- PPARs
- Neopterin

- TNFa, IL-1, TGFβ, MMPs, PDGF, IGF-1, MCP-1

**Local aggravation of arteritis**

- endothelial cells
  - ICAM, VCAM^1^ CCR2, CD40L
  - IL-8, MCP-1
  - Fractalkin/CX3CR1
  - PDGF, Selectins

**oxLDL**

- smooth muscle cells
  - HLA-DR^1^ CD40L^1^
  - AG-presentation^1^ proliferation^1^

- Th1-cells
  - IFNg^1^ TNF^1^ TGFβ^1^ IL-17^1^

- platelets
  - RANTES

- monocytes
  - CXC3^1^ CR1^1^ CCR2^1^ Ly6C^1^ CD14^1^ CD16^1^
  - MCP, M-CSF^1^ CD40L^1^

- oxLDL

- TNFa, IL-1, TGFβ, MMPs, PDGF, IGF

- Inhibition by β-blockers e.g. carvedilol, nebivolol

**Initiation**

- cell injury by oxLDL, diabetes, infection, smoking, oxidative stress etc.

- smooth muscle cells
- HLA-DR^1^ CD40L^1^ AG-presentation^1^ proliferation^1^

- Th1-cells
  - IFNg^1^ TNF^1^ TGFβ^1^ IL-17^1^

- oxLDL

- TNFa, IL-1, TGFβ, MMPs, PDGF, IGF

- Inhibition by β-blockers e.g. carvedilol, nebivolol

Visceral adipose tissue (VAT)

Center of the immune-mediated inflammation

**Figure 2.** Visceral adipose tissue (VAT) from obese mice contains more inflammatory cells than VAT from lean counterparts. LF, low-fat diet; HF, high-fat diet.

**Figure 3.** Accentuated major histocompatibility complex class II levels (I-A<sup>?</sup>) in visceral adipose tissue of obese mice indicate local T lymphocyte activation. LF, low-fat diet; HF, high-fat diet.

Visceral adipose tissue (VAT)
Major responsible for CVD (also in lean people)
Obesity research in Graz

STYJOBS / EDECTA
Cohort

http://www.meduni-graz.at/styjobs/
http://clinicaltrials.gov/ct2/show/NCT00482924
**STYrian Juvenile OBesity Study**

**Early Detection of Atherosclerosis**

**STYJOBS**

- A body mass index spectrum from 10 to 50 kg/m²
- from anorexia to morbid adiposity

**EDECTA**

- **Prediction**
- **Personalisation**
- **Prevention**

**Database Biobank**

- **preclinical** Diagnosis (Theragnosis)
- **new individual** Risk profiles, Genetics
- **Early** Intervention (nutrition?)

- Lipometry
- Adipokines
- Craving
- Lifestyle Aging
- Public Health
- Systems Biology
- IT Networking

- Inflammation
- Atherosclerosis
- Brown / White Adipose Tissue
Lipometry (SAT-TOP)

Complex Database
(>200 variables / proband)
Prospective end size n=1600

Bioresource
Complex anthropometry: **SAT-Distribution** by lipometry®

**Lipometry**

- 5 - front chest
- 3 - biceps
- 7 - upper abdomen
- 8 - lower abdomen
- 11 - front thigh
- 14 - inner thigh
- 6 - lateral chest
- 10 - hip
- 12 - lateral thigh
- 1 - neck
- 4 - upper back
- 2 - triceps
- 9 - lower back
- 13 - rear thigh
- 15 - calf

SAT thickness by infrared method
Patent EP2091415
Adipokines
Low grade inflammation, atherosclerosis, metabolic syndrome, fatty liver, oxStress, craving
Recent Data
STYJOBS / EDECTA
Results – age range overview, sets of variables

Variables
Clinical/Anthropometric/Carotis-sono (82)
Laboratory/Biomarkers/Adipokines (100)
Glucose metabolism, liver, kidney function, lipids, oxidative/nitrosative stress, adipokines, orphane vascular markers, clotting
Genetic/mitochondrial function/miscellaneous (100)
Results, vascular/inflammatory/metabolic markers

- **Carotis IMT**: R=0.58, P<0.01
- **US-CRP**: R=0.34, P<0.01
- **Interleukin-6**: R=0.33, P<0.01
- **BMI**: (-) syst Bloodpressure: R=0.48, P<0.01
- **HOMA-index**: R=0.29, P<0.01
- **Adiponectin**: R=0.25, P<0.01

Mangge et al Atherosclerosis 2009, PMID: 18656877
Mangge et al Obesity 2008, 2010 PMID: 18846045
STYJOBS / Results

Ultrasonography of CCA
Intima Media Thickness (IMT)*

Mangge et al
Exp Clin Endocrinol Diabetes. 2004. PMID: 1523902
Mangge et al Atherosclerosis 2008, PMID: 18656877
Mangge et al Obesity 2009, PMID: 18846045

STYJOBS, age below 18 years, n=523
STYJOBS/Results
IMT ⇔ US-CRP (Inflammation)

STYJOBS, age < 18 years

Weak correlation
R=0.18

p < 0.001
STYJOBS / Results
IMT versus waist

Waist circumference vs Carotis IMT

STYJOBS
age < 18 years

Excellent correlation

R=0.5

Mangge et al Atherosclerosis 2009, PMID: 18656877
Mangge et al Obesity Research 2008, PMID: 18846045
Visceral adipose tissue (VAT)
Center of the immune-mediated inflammation

Figure 2. Visceral adipose tissue (VAT) from obese mice contains more inflammatory cells than VAT from lean counterparts. LF, low-fat diet; HF, high-fat diet.

Figure 3. Accentuated major histocompatibility complex class II levels (I-A^+) in visceral adipose tissue of obese mice indicate local T lymphocyte activation. LF, low-fat diet; HF, high-fat diet.


STYJOBS / Results

Intima media thickness versus transaminases

STYJOBS, age < 20 years, n=523

Mangge et al. exp clin endocrinol diabetes. 2004, PMID: 1523902
Mangge et al. atherosclerosis 2009, PMID: 18656877
Mangge et al. obesity 2008, PMID: 18846045
SAT thickness by infrared method
Patent EP2091415
STYJOBS / Results
IMT versus Anthropometry

<table>
<thead>
<tr>
<th>Modell</th>
<th>R</th>
<th>R-Quadrat</th>
<th>Korrigiertes R-Quadrat</th>
<th>Standardfehler des Schätzers</th>
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<tr>
<td>1</td>
<td>0.586a</td>
<td>0.343</td>
<td>0.338</td>
<td>0.008328</td>
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<tr>
<td>2</td>
<td>0.642b</td>
<td>0.413</td>
<td>0.403</td>
<td>0.007906</td>
</tr>
<tr>
<td>3</td>
<td>0.661c</td>
<td>0.436</td>
<td>0.423</td>
<td>0.007774</td>
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<tr>
<td>4</td>
<td>0.684d</td>
<td>0.467</td>
<td>0.450</td>
<td>0.007588</td>
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<tr>
<td>5</td>
<td>0.701e</td>
<td>0.491</td>
<td>0.470</td>
<td>0.007450</td>
</tr>
</tbody>
</table>

Multiple Regression including BMI, %bodyfat, waist, hip, waist to height ratio, lipo measure points 1-15, Adiponectin subfractions
Neck circumference as a novel measure of cardiometabolic risk: the Framingham Heart study.

Neck circumference is associated with CVD risk factors even after adjustment for VAT and BMI. These findings suggest that upper-body sc fat may be a unique, pathogenic fat depot.

STYJOBS / Results
HMW, MMW, LMW / total adiponectin ratios

High Molecular Weight (HMW) adiponectin oligomer

Medium Molecular Weight (MMW) adiponectin hexamer

Low Molecular Weight (LMW) adiponectin trimer

Oligomerisation disturbed?


Nuchal thickness of subcutaneous adipose tissue is tightly associated with an increased LMW/total adiponectin ratio in obese juveniles. Atherosclerosis, 2009, PMID:18656877
STYJOBS / Results

Adiponectin

Results of a multiple regression

HMW Adiponectin decrease is closely associated with increased carotis IMT

Table 5 Multiple stepwise regression analysis to evaluate correlations of total adiponectin and subfractions

<table>
<thead>
<tr>
<th></th>
<th>β Coefficient</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant (total adiponectin)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Apolipoprotein A1</td>
<td>0.25</td>
<td>0.02</td>
</tr>
<tr>
<td>Carotis IMT</td>
<td>−0.22</td>
<td>0.04</td>
</tr>
<tr>
<td>Uric acid</td>
<td>−0.27</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Constant (H-MW adiponectin) | <0.0001 |     |
| Apolipoprotein A1        | 0.28     | 0.008 |
| Carotis IMT              | −0.35    | 0.001 |
| Uric acid                | −0.27    | 0.01  |

Constant (LMW adiponectin) | <0.0001 |     |
| Carotis IMT              | −0.18    | 0.05  |
| Constant (LMW adiponectin) | <0.0001 |     |
| Oxidized LDL             | 0.27     | 0.008 |

Carotid IMT, carotid intima-media thickness; HMW, high-molecular weight; LDL, low-density lipoprotein; LMW, low-molecular weight; MMW, medium-molecular weight.

Results of a multiple regression

LMW Adiponectin increase is closely associated with nuchal fat thickness

Independent variables chosen by multiple stepwise regression analysis using all variables of Table 3 and adiponectin subfraction ratios as dependent variable

<table>
<thead>
<tr>
<th></th>
<th>β Coefficient</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Obese juveniles, n = 71 and controls, n = 75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nuchal SAT-thickness</td>
<td>0.47</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HMW/total adiponectin ratio</td>
<td>−0.48</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nuchal SAT-thickness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMW/total adiponectin ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nuchal SAT-thickness and biceps</td>
<td>0.56</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SAT-thickness</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Nuchal thickness of subcutaneous adipose tissue is tightly associated with an increased LMW/total adiponectin ratio in obese juveniles. *Atherosclerosis, 2009*, PMID:18656877
Adiponectin
HMW fraction most effective against AS

Szmitko et al
Results of the multiple regression

**Table 3. Results of the multiple regression model including all probands.**

<table>
<thead>
<tr>
<th>Criterion: oxLDL (mg/dl)</th>
<th>Beta</th>
<th>p - value</th>
<th>Adj. R²model (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (N = 797)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>0.504</td>
<td>&lt;0.0001</td>
<td>25.0</td>
</tr>
<tr>
<td>HDL-Cholesterol (mg/dl)</td>
<td>-0.275</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

Independent variables included in this model are gender, age, metabolic syndrome, body mass index, BMI-SDS, waist circumference, hip circumference, waist to height ratio, SAT thicknesses of neck, biceps, lateral chest, upper abdomen determined by lipometry, systolic-, diastolic-blood pressure, carotis communis intima media thickness, glucose, insulin, HOMA-index, triglycerides, cholesterol, HDL-, LDL-cholesterol, fatty acids, homocystein, adiponectin, leptin, AST/GOT, ALT/GPT, gammaGT, cholinesterase, creatinine, uric acid, uratsensitive (US) C-reactive protein.

Mangge et al. High density lipoprotein cholesterol level is a robust predictor of lipid peroxidation irrespective of gender, age, obesity, and inflammatory or metabolic biomarkers. Clinica Chim Acta. 2011, in press.
STYJOBS / EDECTA

Results - **Cardiovascular** risk pattern with emphasis on **BMI, Age, Gender**

- **Carotis IMT**
- **Systolic BP**
- **Diastolic BP**

![Graphs of Carotis IMT, Systolic BP, and Diastolic BP against age for male and female subjects.](image)

- **(−)** Carotis IMT
- **(+)** Age

---

diagnosis
- ○ controls
- ○ obese
Results - Hepatic risk pattern with emphasis on BMI, Age, Gender

- Cholinesterase
- ALT/GPT
- gammaGT

**ALT/GPT cut off**
- Female adult <40 U/L, <15 years < 25
- Male adult <30, <15 years < 25
Consider early development of gender related risk profiles!
HMW adiponectin is decreased in the early phase of vascular abnormalities in obesity.

As the LMW subfraction is increased, and the HMW subfraction decreased, the oligomerisation from LMW to HMW adiponectin may be disturbed.

Trunk weighted obesity is associated with very low HMW adiponectin, and stronger increased carotis IMT.

HDL cholesterol decrease is the best predictor for lipid peroxidation.

Mangge et al Atherosclerosis 2009, PMID: 18656877
Mangge et al Obesity Research 2008, PMID: 18846045
General conclusion

- Obesity is a chronic inflammatory disease.
- Irrespective of sex, age and gender, the inflammatory activation associated with abdominal fat accumulation is crucial for obesity related sequels like atherosclerosis.
- Adipokines are centrally involved in the chronic inflammation of obesity. The balance between the most abundant adipokines, adiponectin and leptin may be crucial for the clinical course of atherosclerosis.
- The “obesity paradox” may be explained by “protective” anti-inflammatory qualities of the adipose tissue. However, abdominal (trunk) obesity abrogates the protective effects.
- Therapeutic modification of chronic low grade inflammation with reference to the individual SAT distribution may become an important challenge for the future.
Conclusion

- Our data show that already the early phase of obesity is associated with chronic inflammation, preatherosclerosis, and an essentially altered adipokine synthesis.

- SAT- distribution (visceral, nuchal) is a crucial risk factor.

Mangge et al. Atherosclerosis, PMID: 18656877, 2009
Mangge et al. Obesity, PMID: 18846045, 2009
Wallner, Mangge et al, PMID:20168310, 2010
Mangge et al Current Med Chem, PMID:21062254, 2010
Fritsch, Mangge et al Atherosclerosis, PMID:21334626, 2011
Mangge, Renner et al, PMID:21318054, 2011
Thank you for the attention!

http://www.meduni-graz.at/styjobs/
http://clinicaltrials.gov/ct2/show/NCT00482924
JUPITER-Trial

Subjects
No history of CAD
LDL-cholesterol < 3.4 mmol/L
CRP > 19.0 nmol/L
Random treatment
Rosuvastatin 20 mg daily or Placebo

Subjects with no history of coronary artery disease, LDL-cholesterol < 3.4 mmol/L, and CRP > 19.0 nmol/L randomly received treatment with rosuvastatin 20 mg daily (n=8,901) or placebo (n=8,901). The primary endpoint included occur-

Figure 5. Jupiter trial primary endpoint: myocardial infarction, stroke, unstable angina/revascularization, cardiovascular death.
Leptin

R = 0.68
P < 0.01
N = 804
Uric acid, HDL-cholesterol...vs BMI

Mangge et al Atherosclerosis 2009, PMID: 18656877
Mangge et al Obesity 2008, PMID: 18846045

R = 0.5
R = 0.28
R = 0.19
R = 0.38
R = 0.29

n.s.
Juvenile Obesity
Reduces life expectancy

Childhood obesity is associated with premature death in adulthood

Followed, obese children (American Indians), not suffering from diabetes.

Childhood **hypertension** was strongly associated with the rate of death from endogenous causes in early adulthood (incidence-rate ratio, 1.57; 95% CI, 1.10 to 2.24).

No significant associations were observed between death rates and childhood **cholesterol** levels*.

STYJOBS / EDECTA
Where we are at the moment
870 probands recruited, 1500 intended

STYJOBS / EDECTA
Scope of recent publications

Nuchal fat, White/Brown AT, Vascular Risk, Adipokines

Hippocampus, Craving, Insulin, SAT distribution

Raggam, Prüller, Mangge et al. Obesity, submitted 2011
Mangge, Fuchs et al. Journal of Obesity, PMID: 21274279 2011
Arnold, Mangge, Strobl et al. Pediatric Research, PMID: 21135756, 2011
Mangge, Fuchs et al. Current Medicinal Chemistry, PMID: 21062254, 2010 Focus
Fritsch, Mangge et al. Atherosclerosis PMID: 20619835, 2010
Wallner-Liebmann, Mangge et al. Obesity PMID: 20168310, 2010
Mangge et al. Obesity, PMID: 18656877, 2009
Mangge et al. Atherosclerosis, PMID: 18846045, 2009
Moeller, Mangge et al. Obesity, PMID: 17495209, 2007
Mangge et al. Exp and Clin Endocrinology & Diabetes, PMID: 15239023, 2004

Future activities
Epigenetics, miRNAs and white/brown AT, Fatty Liver Disease ↔ Nutrition, Modulation of Craving

internet
http://clinicaltrials.gov/ct2/show/NCT00482924
http://www.meduni-graz.at/styjobs

Tackling the early burden in obesity
From 1st decade
From 2nd decade
From 3rd decade
Partners

Medical-, Karl Franzens-, Technical-Universities of Graz


External

Paracelsus Privatuniversität Salzburg
Walter Sperl, Daniel Weghuber, Friedrich Hoppichler, intended cooperation with the University of Munich Reinhard Halle, Sportsmedicine

Boston University School of Medicine, Framingham
Vasan S. Ramachandran
STYJOBS / Results

Interleukin-6

Results of the multiple regression

Fibrinogen is the best predictor for Interleukin-6 irrespective of age, gender, and other biomarkers.

Table 3c. Results of a combined multiple regression model including all probands and all clinical, anthropometric, metabolic/inflammatory variables.

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Beta</th>
<th>p-value</th>
<th>Adj. R² model (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (N = 553)</td>
<td></td>
<td>&lt;0.0001</td>
<td>26.6</td>
</tr>
<tr>
<td>Fibrinogen (mg/dl)</td>
<td>0.004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Independent variables</td>
<td>included in this model are body mass index, BMI-SDS, waist circumference, hip circumference, waist to height ratio, SAT thicknesses of neck, triceps, biceps, upper back, front chest, lateral chest, upper abdomen, lower abdomen, lower back, hip, front thigh, lateral thigh, inner thigh, calf, metabolic syndrome, systolic blood pressure, carotis IMT, US-CRP, HOMA-index, resistin, leptin, adiponectin, triglycerides, cholesterol, HDL-cholesterol, LDL-cholesterol, oxidized LDL-cholesterol, homocystein, ALT-GPT, gammaGT, cholesteraze, uric acid, creatunine, aPTT, endogenous thrombin potential, antithrombin, D-Dimer, fibrinogen</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Carotid intima-media thickening indicates a higher vascular risk across a wide age range: prospective data from the Carotid Atherosclerosis Progression Study (CAPS). Lorenz et al. Stroke, 2006

"Its predictive value is as high in younger subjects as in older subjects"
Metabolic Profiles
Blood pressure

**Box plots**

- **Control**
- **Obese**

**Statistical Significance**
- \( p < 0.01 \)

**Graph**

- **Correlation**
  - \( r = 0.5 \)
  - \( p < 0.001 \)

**References**

- Mangge et al Atherosclerosis 2008, PMID: 18656877
- Mangge et al Obesity Research 2008, in press
Glucose metabolism
Glucose metabolism

HOMA index = \( \text{FI} \times \text{FGlu} : 22.5 \)

\( \text{FI} = \) fasting insulin
\( \text{FGlu} = \) fasting glucose

Glucose mmol/L

Insulin uE/ml

HOMA IR = homeostatic model assessment - insulin resistance

HOMA Index = FI x FGIu : 22.5
FI = fasting insulin
FGIu = fasting glucose
Glucose mmol/L
Insulin uE/ml

HOMA IR = homeostatic model assessment - insulin resistance

Mangge et al
Atherosclerosis
2008, PMID: 18656877
Mangge et al
Obesity Research
2008, in press

Diabetes

p <0.0001
Liver function
STYJOBS/Results

Liver enzymes I

- AST/GOT (UI) NH4 Hep plasma: p = 0.03
- ALT/GPT (UI) NH4 Hep plasma: p < 0.0001
- AST/GOT (UI) NH4 Hep plasma vs. carotis com. intima-media-thickness (cm): n.s.
- ALT/GPT (UI) NH4 Hep plasma vs. carotis com. intima-media-thickness (cm): p < 0.0001, r = 0.35
STYJOBS/Results
Liver enzymes II

- GGT (UI) in NH4 Hep plasma: p < 0.0001
- CHE (UI) in NH4 Hep plasma: p < 0.0001

Correlations:
- p < 0.0001
- r = 0.2
- r = 0.24
Lipids, Uric Acid, Oxidative / Nitrosative “Stress”
STYJOBS/Results
HDL-cholesterol, oxLDL

Mangge H, Pilz S. Journal of Clinical Endocrinology and Metabolism 2005
STYJOBS / Results
Lipid profile, and uric acid

Fatty acids  Triglycerides  VLDL-Cholesterol  Uric acid

- p < 0.001
- p < 0.0001
- p < 0.001
- p < 0.0001
STYJOBS / Results
Total NO (NOX), oLDL

Monocytes
Principal offenders in atherogenesis

Figure 1. Mononuclear phagocytes in atherogenesis.

Obesity in Europe

Adults

BMI ≥ 30

Source: IASO
International Obesity TaskForce

<table>
<thead>
<tr>
<th>Region</th>
<th>BMI Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>England</td>
<td>≥25%</td>
</tr>
<tr>
<td>Scotland</td>
<td>≥25%</td>
</tr>
<tr>
<td>Northern Ireland</td>
<td>≥25%</td>
</tr>
<tr>
<td>Sweden</td>
<td>≥25%</td>
</tr>
<tr>
<td>Finland</td>
<td>≥25%</td>
</tr>
</tbody>
</table>

No Data <10% 10%-14% 15%-19% 20%-24% ≥25%
Obesity in Europe

Juveniles

Kids around 10 years*

Source: IASO
International Obesity TaskForce
Adiponectin Receptors

Antinflammatory effect

modified from Tilg H., Moschen A.: Nature Review Immunology, 6:772-83, 2006
IP-10, Mig, and I-TAC are expressed in MΦ, endothelial cells, and smooth muscle cells in vasculature. They recruit T-lymphocyte migration, important for the development of atheromata.

**Inhibition of of CXCR3 chemokine ligand expression**

*Adiponectin reduces IP-10, Mig, and I-TAC mRNA levels in human MΦ*
Obesity in Europe

Adults

BMI ≥ 30

Source: IASO International Obesity TaskForce

<table>
<thead>
<tr>
<th>No Data</th>
<th>&lt;10%</th>
<th>10%–14%</th>
<th>15%–19%</th>
<th>20%–24%</th>
<th>≥25%</th>
</tr>
</thead>
</table>

Medical University of Graz
Obesity in Europe
Juveniles

Kids around 10 years*

Source: IASO
International Obesity TaskForce