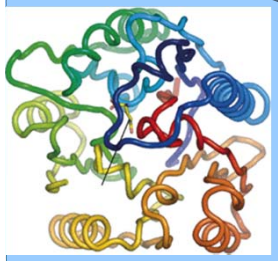

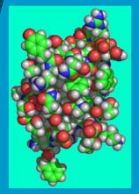

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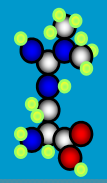
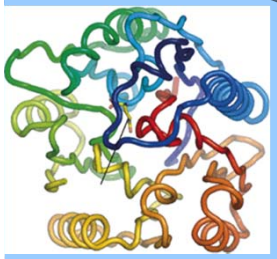
Serum Insulin & Blood Pressure in Obesity may be Linked to Subcutaneous & Omental Fat ADMA Content



P A Sufi[1], D Heath[1], K Mcdougall[1], L Jones[1], V Mohamedi[2]

1. Whittington Hospital & 2. UCL



Context

- Obesity is an excess of adipose tissue (fat).
- It is the most prevalent nutritional disorder associated with significantly increased risk for CVD morbidity and mortality.
- The exact role and mechanisms by which obesity promotes cardiovascular risk is poorly understood.
- Obesity is associated with adverse changes in circulating CVD risk factors, which may be involved in the development of T2DM and CVD.

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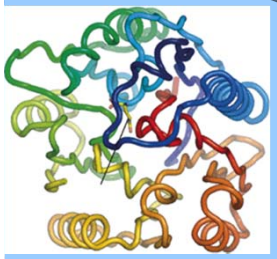
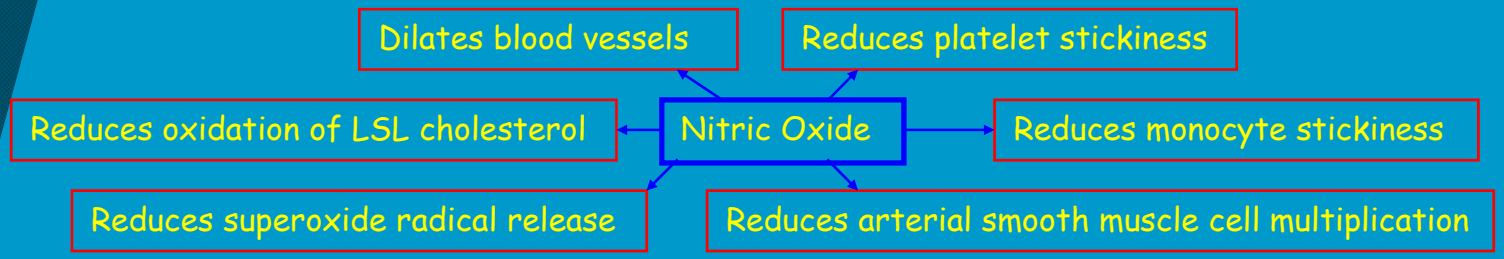


Metabolic Syndrome & NO



- Endothelial function determined by bioavailability of NO, and insulin sensitivity modulated by adiposity and altered NO levels, may explain both the endothelial dysfunction and insulin resistance of obesity.
- Although it has been postulated that adipose tissue-derived mediators (leptin, TNF-a, IL-6 and adiponectin) act on the endothelium to produce detrimental effects, to date none has been clearly identified.
- Asymmetric dimethylarginine (ADMA) – a metabolic by-product of protein modification in the cytoplasm - is an endogenous inhibitor of all forms of nitric oxide synthase (NOS) and is found in plasma.

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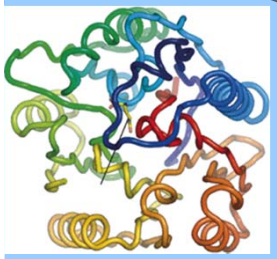

ADMA inhibition of NO:

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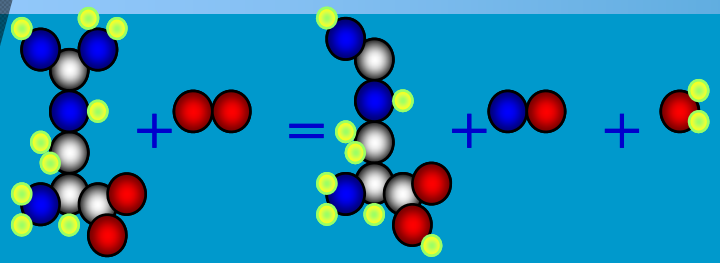

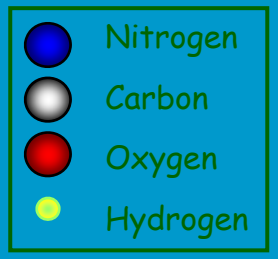

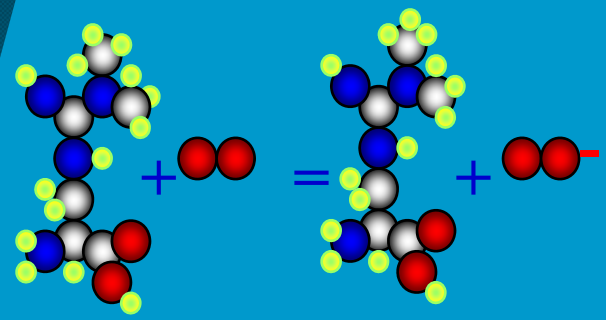

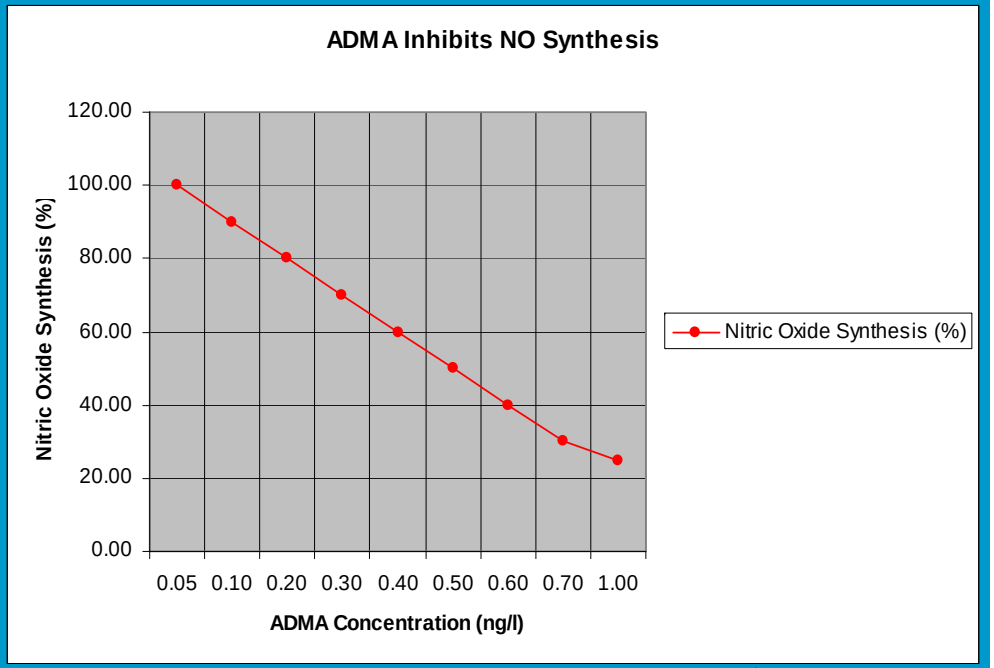

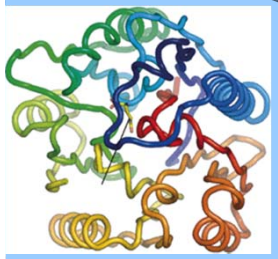

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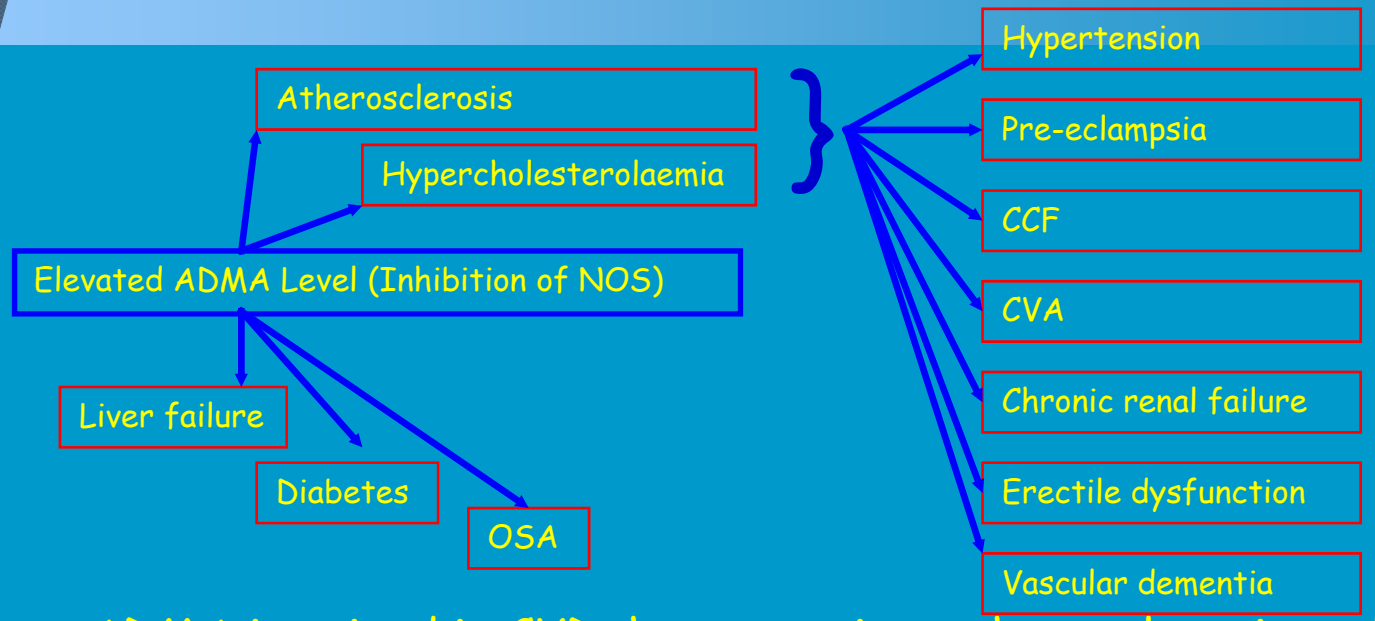
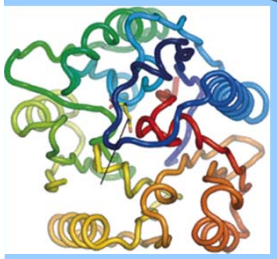
Effects of ADMA

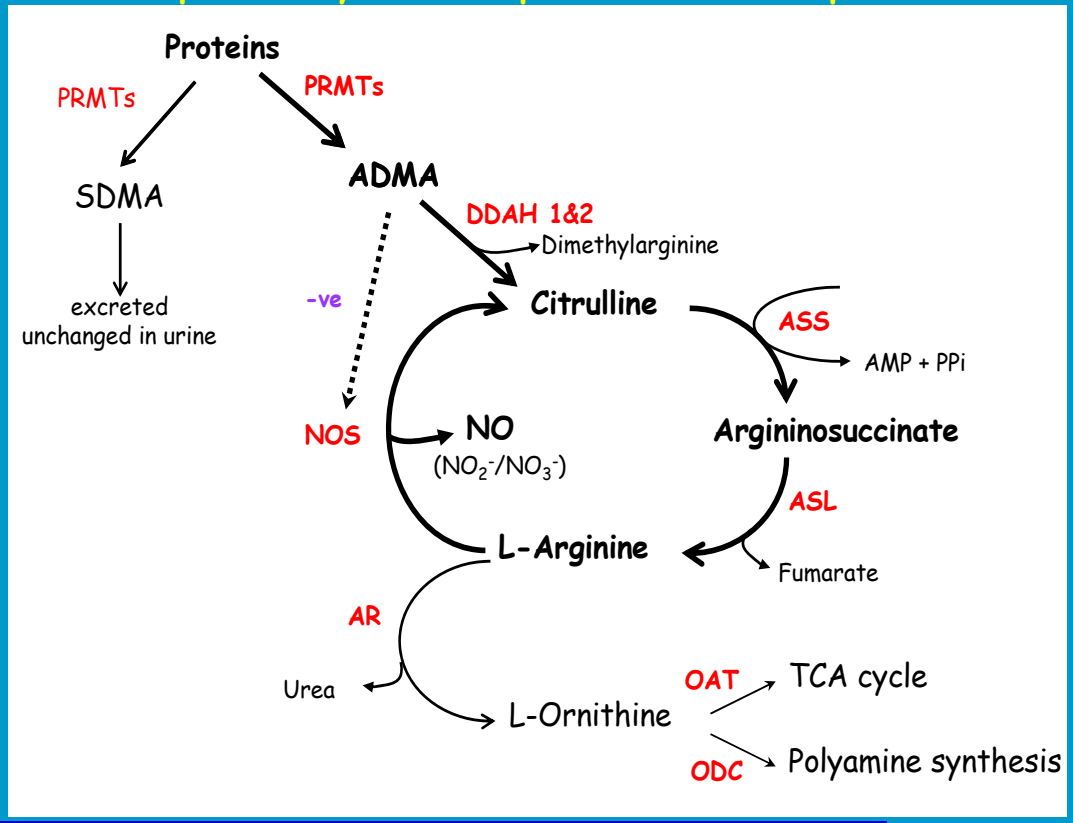


- Plasma ADMA is raised in CVD, hypertension, atherosclerosis and T2DM.
- ADMA levels are also elevated in morbidly obese subjects.
- Circulating ADMA levels correlate closely with degree of insulin resistance and is independently associated with BMI.
- Significant reduction in systemic ADMA, along with improvement in several components of the metabolic syndrome, follows bariatric surgery and weight loss.

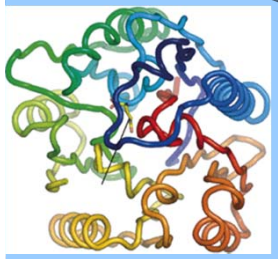


ADMA/DDAH Pathway

- ADMA is synthesized by PRMTs and hydrolysed by DDAH: all components of this pathway are expressed in adipose tissue.



PRMT: protein arginine methyl transferase; DDAH: dimethylarginine dimethylaminohydrolase;
ASS: argininosuccinate synthase; ASL: argininosuccinate lyase; AR: arginase;
NOS: nitric oxide synthase; OAT: ornithine aminotransferase; ODC: ornithine decarboxylase



Aims

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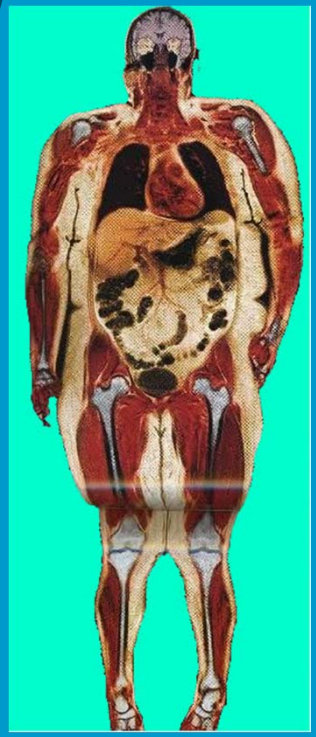
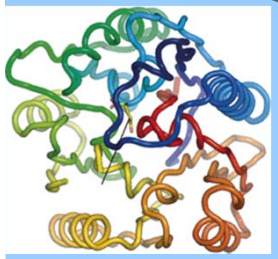


To investigate the

- depot-specific differences in ADMA content and release, and
- the expression of DDAH 1 & 2 (the enzymes responsible for ADMA hydrolysis) and PRMTs (the enzymes responsible for the synthesis of ADMA)

in human omental and subcutaneous adipose tissue.

PRMT: protein arginine methyl transferase; DDAH: dimethylarginine dimethylaminohydrolase;



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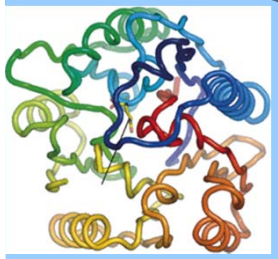
Method

- A cross-sectional cohort study of Caucasian morbidly obese, non-diabetic female patients undergoing gastric banding or cholecystectomy
- Circulating, adipose tissue content and generation of ADMA and tissue expression of DDAH-1 and -2 mRNA, and PRMT-3 protein were determined from omental and subcutaneous depots.
- In a subgroup of patients (n=9) the stroma-vascular fraction was separated from whole adipose tissue and ADMA and DDAH were analysed.
- Insulin resistance was assessed by HOMA-IR and body fat content by electrical bio-impedance.
- *Exclusion: DM, CHD, HTN, conditions or agents affecting cytokine release e.g; aspirin, NSAIDs, steroids, warfarin, ACE inhibitors, statins*

HOMA-IR: Homeostatic Model Assessment-Insulin Resistance
=fasting plasma insulin (μIU/mL) x fasting plasma glucose (mmol/L) / 22.5



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Schema of Methods

Anthropometric Measurements (Body stat analyser)

Fasting Blood

Fat biopsy at surgery

- BMI
- % Body Fat
- % lean Mass

- Lipids
- Glucose
- Insulin

} HOMA-IR

- ADMA

- Tissue ADMA
- Organ Culture ADMA

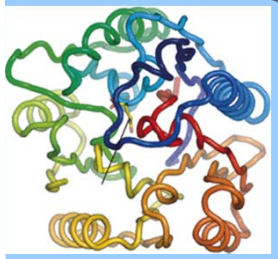
} HPLC

- Stroma-Vascular Fraction (SVF) separated

- mRNA for DDAH
- Protein for PRMT

HPLC: High performance liquid chromatography

Anthropometric and Metabolic Characteristics of Patients



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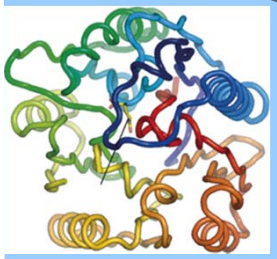
Number	16
Age (years)	43.4 (7.9)
BMI (kg/m^2)	43.8 (10.1)
Body fat (%)	52.6 (7.0)
Lean mass (%)	47.4 (7.0)
Insulin (MU/l)	7.7 (7.1 - 15.0)
Glucose	5.18 (0.45)
Total Cholesterol (mmol/l)	4.56 (0.93)
HDL cholesterol (mmol/l)	1.21 (0.24)
LDL cholesterol (mmol/l)	2.8 (0.92)
Triglycerides (mmol/l)	1.12 (0.32)
ADMA (mM)	1.95 (1.05 - 2.06)
Adiponectin (mg/ml)	5.6 (2.2 - 13.3)
Leptin (ng/ml)	28.7 (18.2 - 40.7)
IL-6 (pg/ml)	2.22 (1.38 - 2.39)
MCP-1 (pg/ml)	221.3 (173.0 - 244.4)
RANTES (ng/ml)	57.0 (35.1 - 66.9)



Results 1

- Serum insulin and systolic blood pressure correlated directly with subcutaneous ADMA content.
- ADMA release was significantly higher from the omental depot (p=0.025) and correlated with BMI.
- While DDAH2 expression was higher compared to DDAH1 in both the whole adipose tissue and the stroma-vascular fraction of both depots
- No depot-specific difference in the expression of either isoform was detected.
- However, PRMT-3 protein expression was higher in the omental compared to the sub-cutaneous adipose tissue.

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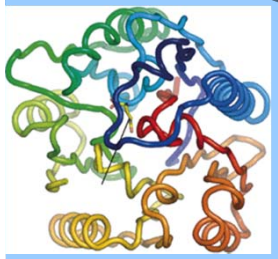

ADMA Release

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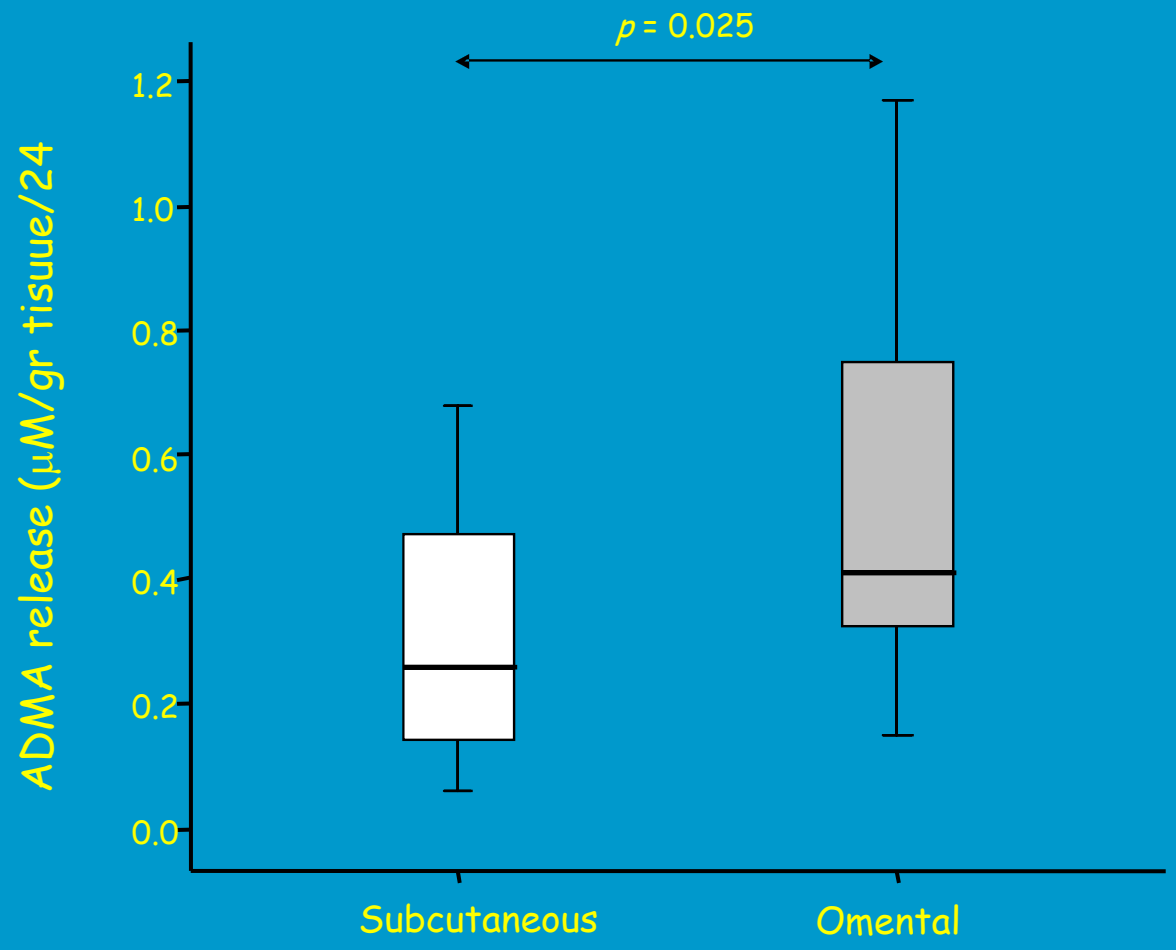
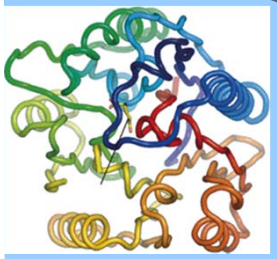


n=13, Comparison by Wilcoxon Rank test



DDAH Expression – Adipose Tissue

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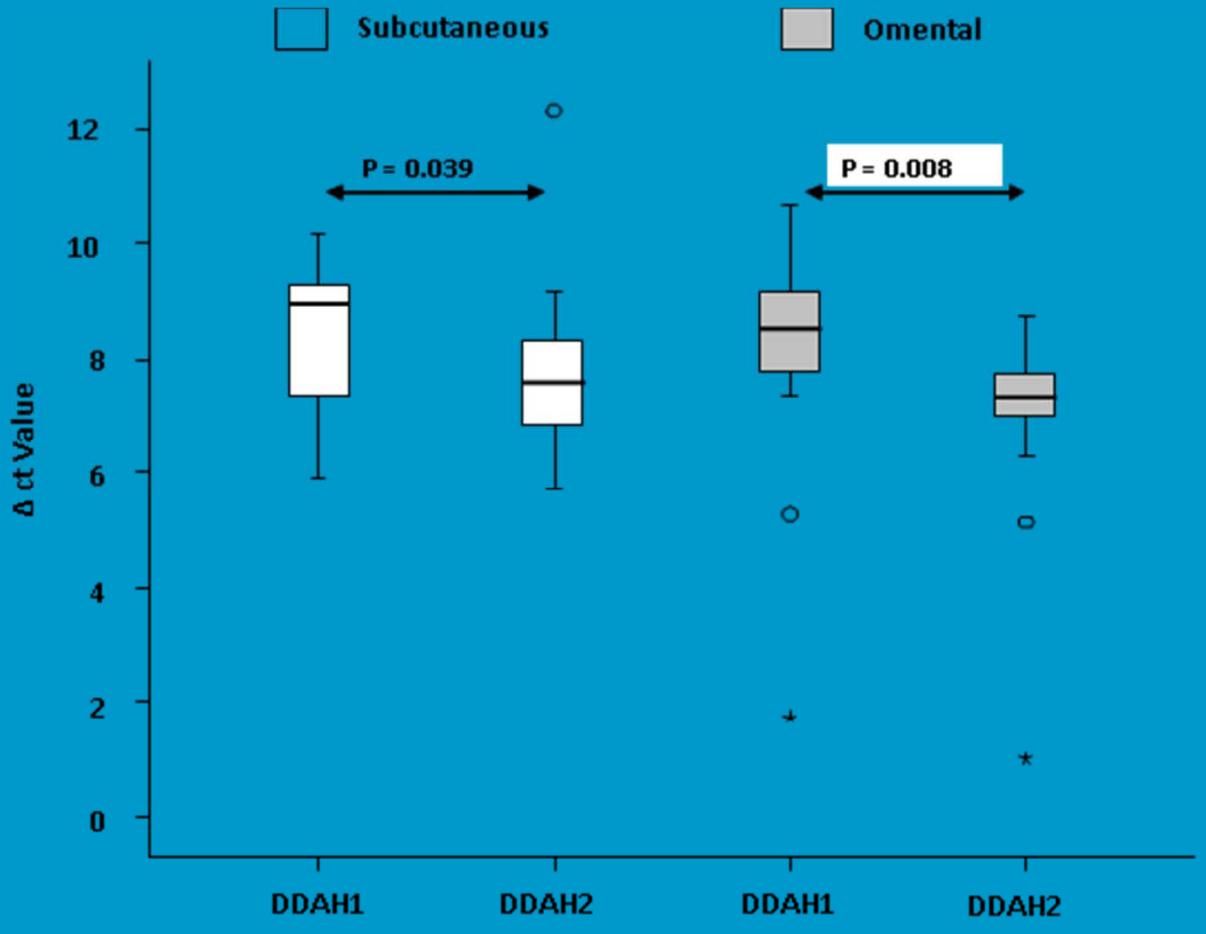
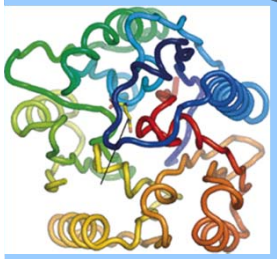


n=15, Comparisons by Wilcoxon Rank test



DDAH Expression – Adipose Tissue vs SVF

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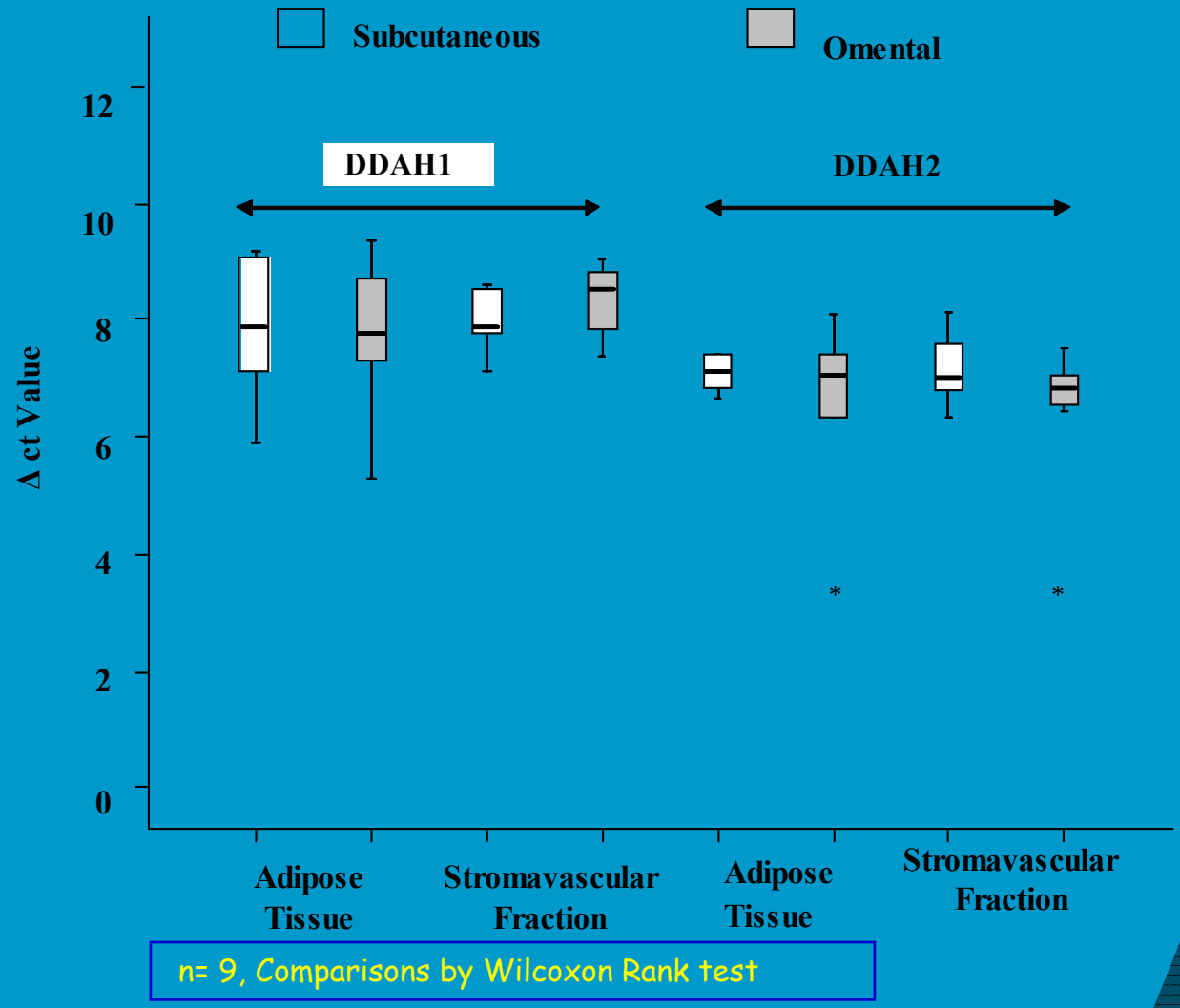
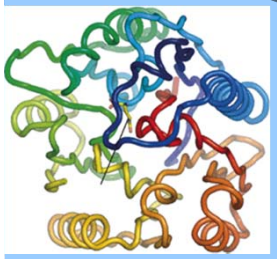
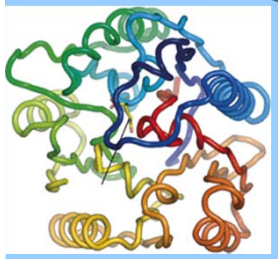




Results 2

- Om ADMA release α BMI ($r = 0.56$, $p = 0.04$)
- HOMA-R α Sc tissue ADMA ($r = 0.83$, $p = 0.04$)
  Om tissue ADMA ($r = 0.70$, $p = 0.08$)

OM: Omental; SC: Subcutaneous; HOMA-IR: Homeostatic Model Assessment-Insulin Resistance



Conclusion

- The direct associations of omental ADMA release and BMI and higher omental ADMA content points to a link between visceral obesity and endothelial dysfunction.
- The depot-specific generation in ADMA may be due to differences in the synthetic enzymes or to changes in the activity, rather than mRNA expression, of DDAH.
- Modulation of adipose ADMA generation may reduce obesity associated co-morbidities.

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