

## Vascular function and adiponectin during puberty in adolescents with obesity

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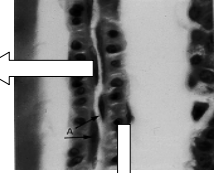
19<sup>th</sup> ANZOS Scientific Meeting Melbourne 2009

## Vascular function

Endothelial cells

PRODUCE

Nitric oxide



Smooth muscle cells

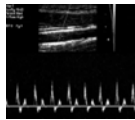
REACT to nitric oxide

VASODILATATION

Endothelial dysfunction is a key and early event in the development of atherosclerosis

Ross R, Nature 1993

## Vascular function evaluation



Changes in blood flow

Flow mediated dilatation

FMD

Endothelial Function



Nitric oxide



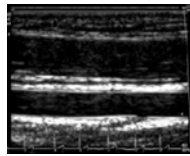
Glyceryl Trinitrate

GTN mediated dilatation

GTN

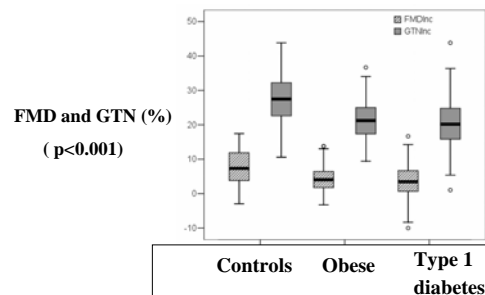
Smooth Muscle Function

VASODILATATION



Brachial artery

## Vascular dysfunction (FMD & GTN) in children with obesity



Peña A et al, J Clin Endocrinol Metab 2006

## Vascular function (FMD & GTN)

In adults

FMD correlates with coronary angiography & predicts risk of atherosclerosis

Anderson et al, JAAC 1995

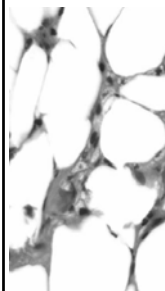
Shechter M et al, Int J Cardiol 2008

GTN is reduced in adults with coronary artery disease

Adams et al, J Am Coll Cardiol 1998

Raitakari OT et al, Am J Cardiol 2001

## Total & High Molecular Weight (HMW) adiponectin



- Decreased in obesity
- Metabolic/anti-inflammatory effects
- Vascular endothelial effects
- HMW & LMW adiponectin levels change during puberty

Stefan N et al, Horm Metab Res 2002

Pena et al, Internat J Ped Obesity 2009

Andersen KK, J Clin Endocrinol Metab 2007

## Hypothesis

Vascular function and adiponectin levels deteriorate during puberty in children with mild to moderate obesity

## Aim

To evaluate vascular function and adiponectin during puberty in healthy children and children with obesity

## Methods - Subjects

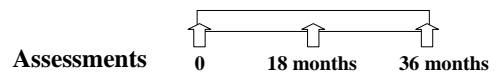
28 healthy children  
30 obese children \* (BMI z score  $2.36 \pm 0.05$ )  
13.1  $\pm$  2.01 years (31/58 males)

### Exclusion criteria

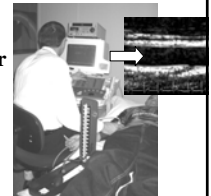
- Syndromal or endocrinological obesity
- Diabetes
- Vitamins, Omega 3 supplements
- ACE inhibitors or statins
- Smoking

\* BMI >95% - 2000 CDC growth charts

## Methods – Longitudinal study

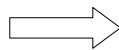


- Vascular function - FMD Flow mediated dilatation  
GTN GTN mediated dilatation
- Serum adiponectin isomers  
Total, HMW, MMW & LMW
- Height, weight, BMI z-score, Tanner
- Blood pressure
- Hs CRP
- Fasting lipid profile
- Glucose, insulin, HbA1c & OGTT



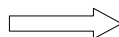
## Statistical analysis

- Student t-test
- Mann-Whitney test



Differences between groups

- Linear mixed model
- GEE



Repeated measurements

## Results - Baseline characteristics

	Obese (n=30)	Controls (n=28)	p
Age (y)	13.2 (2.2)	12.8 (3.0)	0.6
Sex (M/F)	17/13	14/13	0.8
BMI Z score	2.3 (0.2)	0.3 (0.9)	<0.001
Waist (cm)	101 (11)	68 (10)	<0.001
Systolic BP (mm Hg)	113 (8)	108 (7)	<0.001
Diastolic BP (mm Hg)	59 (6)	59 (5)	0.9
Hs CRP (mg/L) *	2.2 [0.4-15]	0.53 [0.3-5]	<0.001
tHcy (umol/L)	6.9 (1.8)	7.2 (2.7)	0.7
Triglycerides (mmol/L)	1.0 (0.6)	0.59 (0.3)	0.005
HDL (mmol/L)	1.1 (0.2)	1.45 (0.4)	0.001
LDL (mmol/L)	2.9 (0.8)	2.6 (0.8)	0.2
Glucose (mmol/L)	4.9 (0.3)	4.7 (0.4)	0.08
Insulin (uU/ml)	23.2 (13.5)	8.4(5.4)	<0.001
HOMA IR *	4.4 [0.6-12]	1.5[0.8-4.2]	<0.001
HbA1c (%)	4.9 (0.8)	5 (0.3)	0.9

Mean (SD) \* geometric median [range]

## Results - baseline characteristics vascular function & adiponectin

	Obese (n=30)	Controls (n=28)	p
FMD (%)	3.7 (3.6)	6.4 (4.3)	<0.001
GTN (%)	21.0 (6.7)	28.8 (6.6)	<0.001
Vessel diameter (cm)	0.29 (0.04)	0.25 (0.03)	<0.001
Total adiponectin (ug/ml) *	6.4 [3.1-12]	7.4 [2.9-13]	0.008
HMW adiponectin (ug/ml) *	2.4 [0.6-6.1]	3.3 [0.5-7.8]	0.007
LMW adiponectin (ug/ml) *	2.1 (0.6)	1.9 (0.6)	0.005

Mean (SD) \* geometric median [range]

## Results over 3 years – Obese children

4/30 Impaired glucose tolerance  
No subject developed diabetes

	Baseline (n=30)	18 m visit (n=29)	36 m visit (n=24)	p
Age (y)	13.2 (2.2)	15.4 (2.2)	16.2 (2.3)	<0.001
Acanthosis nigricans	13	18	17	0.007
HOMA IR	4.4 [0.6-12]	5.5 [1.4-15]	5.4 [1.9-32]	0.08
Waist (cm)	101	104	105	0.01
Hip (cm)	110	117	119	<0.001
Metabolic syndrome **	3	1	5	0.15

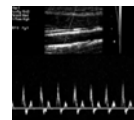
Mean (SD), geometric median [range]

\*\* Weiss R et al, N Engl J Med 2004

## Changes over 3 years in cardiovascular risk

	Obese	Controls
Systolic blood pressure	↑ (p<0.001)	↑ (p=0.02)
Diastolic blood pressure	↑ (p=0.02)	No change
Glucose	↑ (p=0.03)	No change
HOMA IR	No change	No change
LDL cholesterol	↓ (p<0.001)	↓ (p=0.007)
HDL cholesterol	No change	↑↓ (p=0.008)
Triglycerides	↑ (p0.05)	↑ (p=0.06)
Homocysteine	↑ (p<0.001)	↑↓ (p=0.02)
Hs CRP	No Change	No Change

## Vascular function evaluation



Changes in blood flow

Flow mediated dilatation

FMD

Endothelial Function

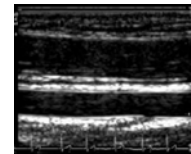


Nitric oxide



Glyceryl Trinitrate

VASODILATION



Brachial artery

GTN mediated dilatation

GTN

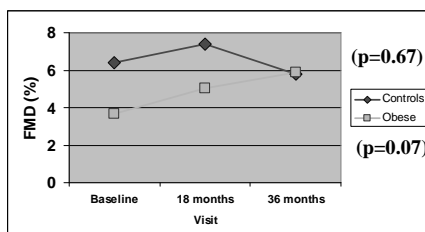


Smooth

Muscle

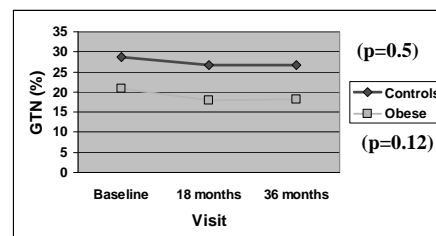
Function

## Endothelial function (FMD) over 3 y



FMD was lower in obese children over time (p=0.02)

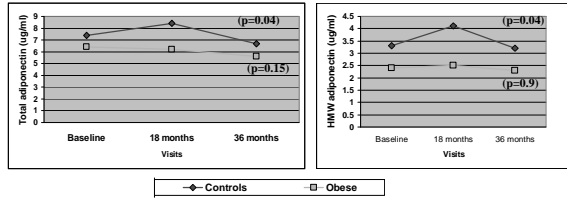
## No change in smooth muscle function (GTN)



Significant difference between obese & controls at all visits (p<0.001)

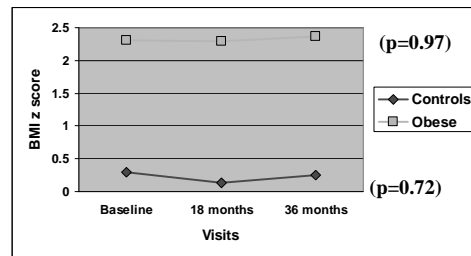
## Adiponectin (total & HMW)

Change in controls, but no change in obese



Significant difference between obese & controls at all visits (p=0.04)

## No change in BMI z score



Significant difference between obese & controls at all visits (p<0.001)

## Adiponectin associations over 3 y in obesity

Adiponectin (total/HMW) related to

- Smooth muscle function [GTN] (p=0.006)
- Brachial vessel diameter (p=0.007)
- Weight z score (p=0.02)
- Waist (p=0.04)
- HDL cholesterol (p=0.04)
- Fasting glucose, insulin & HOMA-IR (p<0.05)
- Puberty (p=0.002)

## Conclusions

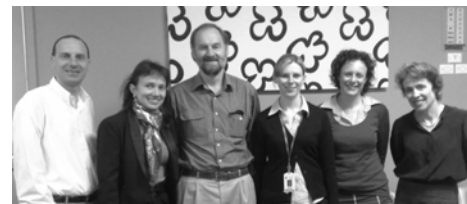
- Vascular function remains stable during puberty in children with mild to moderate obesity while BMI and adiponectin do not change.
- Adiponectin changes during puberty are different in obese children compared to controls.
- Adiponectin might regulate vascular changes during puberty.

## Acknowledgments

- Diabetes Australia & JDRF RACP Fellowships
- NHMRC grant
- APEG Novo Nordisk grant 2007
- Children in the study



Vascular Research team



L Pianto, R Gent, K Gaskin, Dr J Harrington, Dr J Couper

Statisticians C Hirte & P Baghurst



**La siesta, FERNANDO BOTERO**  
Medellin, Colombia - 1932



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Sex (M/F)	17/13	14/13	0.8
Puberty (pre, intra & post)	7/20/3	12/8/8	0.02
BMI Z score	2.3 (0.2)	0.3 (0.9)	<0.001
Waist (cm)	101 (11)	68 (10)	<0.001
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HDL (mmol/L)	1.1 (0.2)	1.45 (0.4)	0.001
LDL (mmol/L)	2.9 (0.8)	2.6 (0.8)	0.03
Glucose (mmol/L)	4.9 (0.3)	4.7 (0.4)	0.036
Insulin (uU/ml)	23.2 (13.5)	8.4(5.4)	<0.001
HOMA IR *	4.4 [0.6-12]	1.5[0.8-4.2]	<0.001
HbA1c (%)	4.9 (0.8)	5 (0.3)	0.1

Mean (SD) \* geometric median [range]