Vascular function and adiponectin during puberty in adolescents with obesity

Alexia Sophie Peña

J Harrington
A Pollard
R Gent
L Piotto
K Gaskin
C Hirte
J Couper

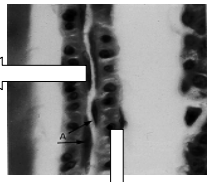
19th ANZOS Scientific Meeting Melbourne 2009

Vascular function

Endothelial cells

PRODUCE

Nitric oxide



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

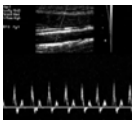
Ross R, Nature 1993

Smooth muscle cells

REACT to nitric oxide

VASODILATATION

Vascular function evaluation



Changes in blood flow

Flow mediated dilatation

FMD

Endothelial Function

Nitric oxide

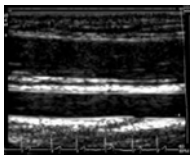
Glyceryl Trinitrate

GTN mediated dilatation

GTN

Smooth Muscle Function

VASODILATATION

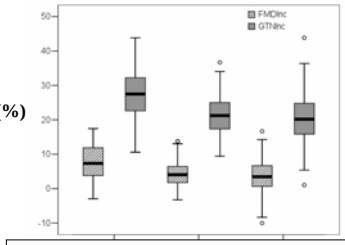


Brachial artery

Vascular dysfunction (FMD & GTN) in children with obesity

FMD and GTN (%)

(p<0.001)



Controls **Obese** **Type 1 diabetes**

Peña A et al, J Clin Endocrinol Metab 2006

Vascular function (FMD & GTN)

In adults

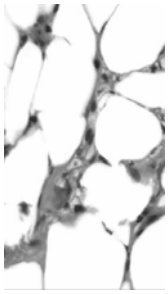
FMD correlates with coronary angiography & predicts risk of atherosclerosis

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 ± 0.05)
13.1 ± 2.01 years (31/58 males)

Exclusion criteria

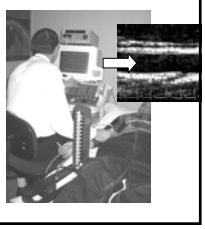
- **Syndromal or endocrinological obesity**
- **Diabetes**
- **Vitamins, Omega 3 supplements**
- **ACE inhibitors or statins**
- **Smoking**

**** BMI >95% - 2000 CDC growth charts***

Methods – Longitudinal study

Assessments **0** **18 months** **36 months**

- **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

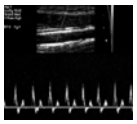
Mean (SD), geometric median [range]

*** 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



Nitric oxide

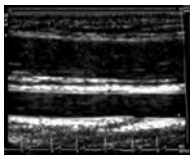
Glyceryl Trinitrate

GTN mediated dilatation

GTN

Smooth Muscle Function

VASODILATATION



Brachial artery

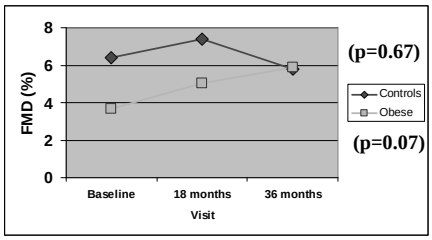
Changes in blood flow

Flow mediated dilatation

FMD

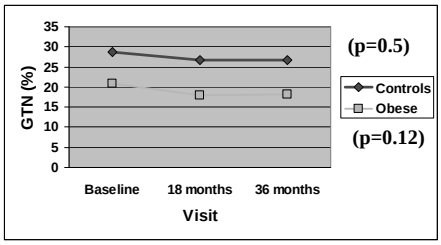
Endothelial Function

Endothelial function (FMD) over 3 y



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

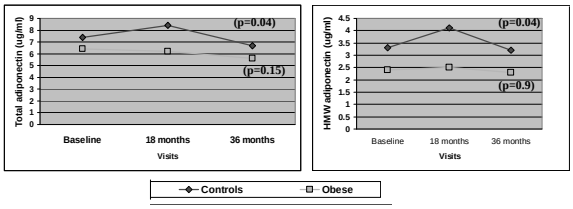
No change in smooth muscle function (GTN)



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

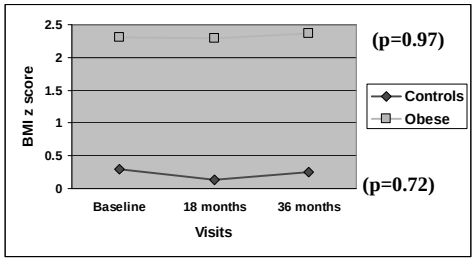
Adiponectin (total & HMW)

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.**

Acknowlegments

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

Vascular Research team

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

Statisticians C Hirte & P Baghurst

La siesta, FERNANDO BOTERO
Medellin, Colombia - 1932

	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**
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**
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)	**0.03**
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]