



Novel uncoupling protein-1 (UCP1) expression in white adipocytes of subcutaneous abdominal adipose tissue in children and adolescents: a protective mechanism for metabolic equilibrium?

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Introduction

➤ Morbid childhood obesity predisposes to metabolic disorders such as diabetes type 2.

➤ Two distinct types of Adipose Tissue are present (Figure 1):

• White Adipose Tissue (WAT, unilocular, energy storage adipocytes)

• Brown Adipose Tissue (BAT, multilocular, heat producing) identified as:

- ✓ Classic BAT (myf5 progenitors)
- ✓ Brown-like multilocular adipocytes interspersed in WAT ("BRITE" or beige)

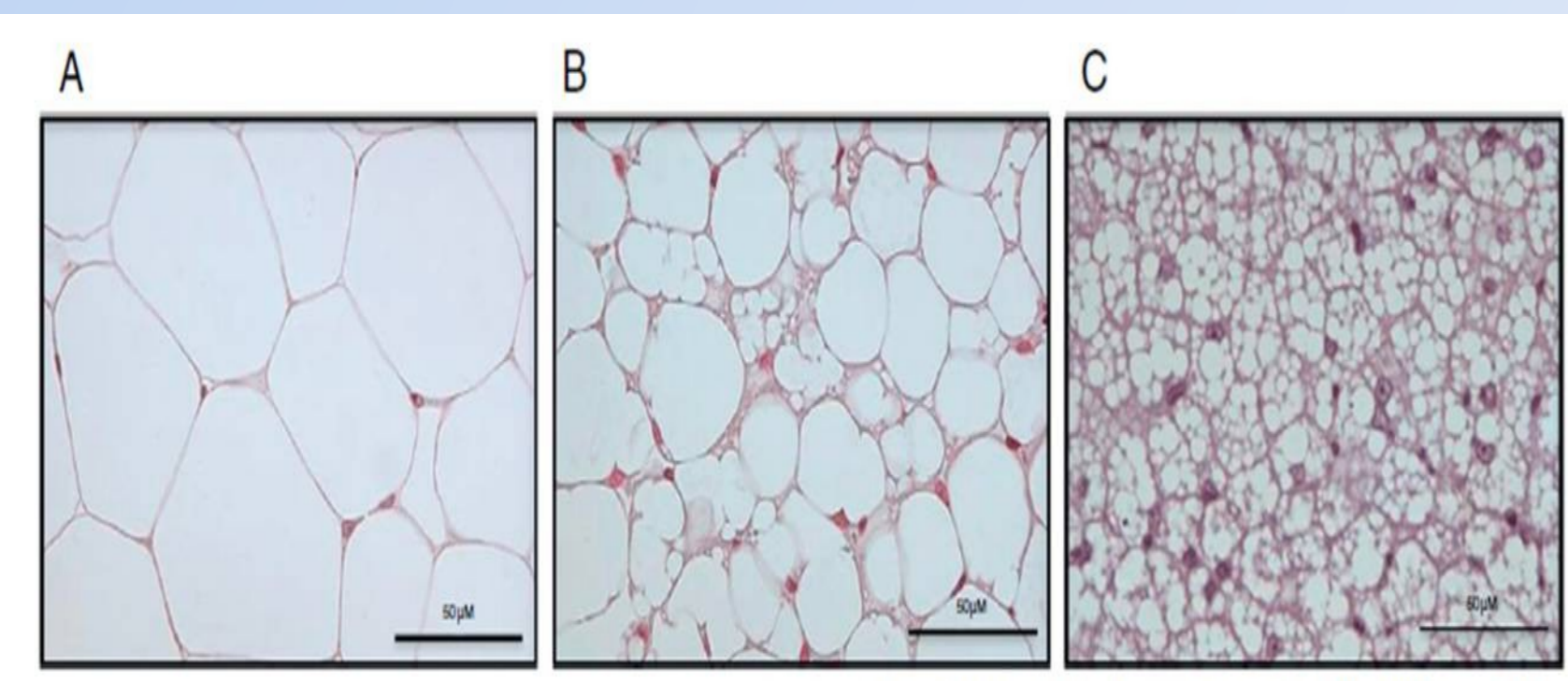


Figure 1: Adipose tissue morphology (A) WAT, (B) BRITE/Beige and (C) BAT

➤ UCP1 is an integral membrane protein "unique" to brown adipocyte mitochondria, where it acts to uncouple oxidative phosphorylation in the inner mitochondrial membrane.¹

➤ In mice, an increased content of UCP1 in adipose tissue mitochondria is strongly linked to protection against diet-induced obesity and heat-producing "BRITE" adipocytes can suppress weight gain and metabolic disease through the action of UCP1.²

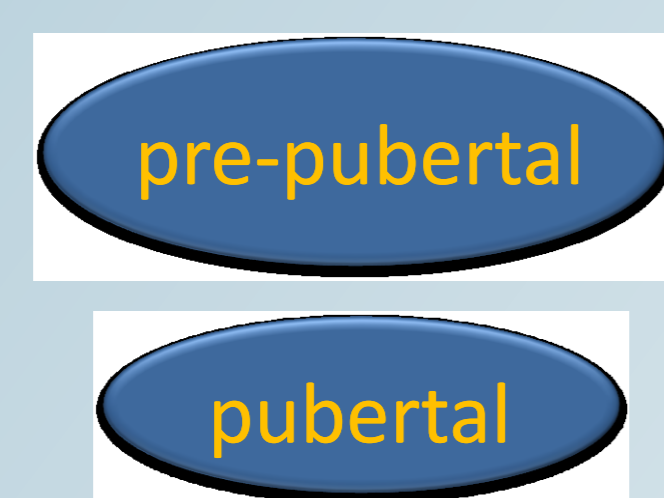
➤ Human obesity is also associated with a reduced expression of UCP1 and other thermogenesis related genes in WAT depots.³

Methods & Materials

➤ Paraffin embedded subcutaneous abdominal adipose tissue microarrays were developed from surgical biopsies of 33 lean (BMI<85%) & 29 obese (BMI≥95%) pre-pubertal children and adolescents.

➤ The children were divided into three age-groups:

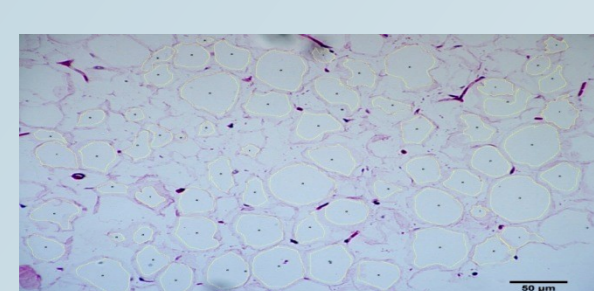
- Group A: 2 mos -7 yrs
- Group B: 8-12 yrs



- Group C: 10-15 yrs

➤ Staining (brown) intensity and distribution of UCP1 (εταιρία αντισώματος) were studied with immunohistochemistry.

➤ mean adipocyte size and total number were estimated by image analysis (adiposoft).



Results

Table 1	Group A		Group B		Group C	
	Lean	Obese	Lean	Obese	Lean	Obese
N	8	8	13	5	13	17
F ¹ /M ²	1/7	1/7	6/7	2/3	2/11	3/14
Tanner	I	I	I	I	II-IV	II-IV
Age (yrs)	2,76 ± 1,94	2,94 ± 1,93	9,55 ± 2,04	10,13 ± 1,62	12,42 ± 0,98	11,45 ± 1,37
BMI (Kg/m ²)	15,99 ± 1,58	18,95 ± 3,71	17,5 ± 2,34	23,38 ± 1,29	20,30 ± 1,90	26,73 ± 4,57
BMI SDS ³	-1 ± 1,31	1,5 ± 0,92*	-0,19 ± 0,99	1,7 ± 0,44*	0,59 ± 0,6	2,25 ± 0,61*
BMI%	26,0 ± 31,45	93,5 ± 3,74**	46,46 ± 27,80	93,2 ± 5,49**	71,0 ± 20,54	95,7 ± 4,21**
WC (cm)	46,0 ± 7,87	53,83 ± 11,09	60,77 ± 10,28	68,2 ± 13,89	70,46 ± 7,9	77,93 ± 12,8 #
WC%	40,0 ± 29,72	90,0 ± 7,74	68,0 ± 36,9	69,6 ± 40,19	75,77 ± 28,41	90,22 ± 20,12
Birth Weight	3,33 ± 0,93	3,62 ± 0,40	3,24 ± 0,46	2,82 ± 0,58	3,38 ± 0,47	3,55 ± 0,42
Gestational Age						
AGA ⁴	4	6	12	3	10	14
SGA ⁵	2	0	0	2	0	0
LGA ⁶	2	2	1	0	3	3
Family History						
Type 2 Diabetes	1	1	4	1	2	6
Obesity	1	2	4	3	8	7

Data are means ± SD or percentages unless otherwise indicated.
* p < 0.002, ** p < 0.001 & # p = 0.04 vs respective lean,
Abbreviations: ¹Female, ²Male, ³SD scores normalized for age and gender, ⁴appropriate for gestational age, ⁵small for gestational age, ⁶large for gestational age

Adipocyte Size (µm)	Group A		Group B		Group C	
	Lean	Obese	Lean	Obese	Lean	Obese
	30.31 ± 13.89	32.09 ± 5.07	34.36 ± 9.90	36.44 ± 8.19	39.59 ± 7.56	39.46 ± 0.42
Number of adipocytes per field	Group A		Group B		Group C	
	Lean	Obese	Lean	Obese	Lean	Obese
	131.25 ± 34.23	118.57 ± 49.10	106.1 ± 34.67	96.0 ± 42.01	105.12 ± 21.29	80.25 ± 30.29

Table 2	Group A		Group B		Group C	
	Lean	Obese	Lean	Obese	Lean	Obese
Glucose (mg/dl)	88,4 ± 5,68	90,5 ± 9,64	96,42 ± 15,5	95,4 ± 7,2	94,1 ± 8,1	97,5 ± 13,20
Total Cholesterol (mg/dl)	155,5 ± 20,41	131,57 ± 20,71	144,25 ± 27,7	145,0 ± 28,4	156,5 ± 27,79	140,0 ± 27,97
HDL (mg/dl)	49,13 ± 13,5	45,3 ± 15,45	55,99 ± 22,25	61,6 ± 13,57	64,92 ± 17,16	53,37 ± 16,32
LDL (mg/dl)	86,75 ± 20,97	74,55 ± 14,29	68,51 ± 12,75	85,7 ± 9,16	68,96 ± 15,04	67,53 ± 14,66
Triglycerides (mg/dl)	67,2 ± 23,7	58,57 ± 28,48	67,54 ± 23,31	59,6 ± 11,5	47,6 ± 15,87	61,5 ± 15,34
Insulin (µU/ml)	2,55 ± 0,59	0,62 ± 0,1*	11,59 ± 6,99	17,19 ± 4,08**	10,76 ± 10,13	15,93 ± 12,76**
HOMA-IR	0,56 ± 0,01	0,13 ± 0,02	2,76 ± 0,27#	4,37 ± 1,36#	2,83 ± 3,00	3,11 ± 2,03#
HMW adiponectin (µg/ml)	8,665 ± 3,95	2,38 ± 0,94*	1,38 ± 0,77\$	1,82 ± 0,82	2,21 ± 1,17\$	1,51 ± 1,38

Data are means ± SD or percentages unless otherwise indicated.
p < 0.04 vs respective lean,
** p < 0.02 vs obese children of group A,
p < 0.03 vs lean and obese children of group A

■ Adipocyte size and number did not differ between the lean and obese children of each group, although size tended to increase with age, but did not exceed 50µm.

■ UCP1 was expressed in the mitochondria of morphologically white adipocytes in all groups without typical beige multilocular lipid droplet morphology. (Figure 3)

■ The lean and obese prepubertal children (A to D) expressed UCP1 with a higher distribution (>50% of tissue) compared to the lean and obese adolescents (E & F) (p=0.01).

- UCP1 intensity was high in:
 - 100% of Group A lean and 50% of Group A obese,
 - 100% of Group B lean and obese and
 - 67% of lean and 54% of obese adolescents, (p=0.022).

Table 4	UCP1 Intensity	Group A		Group B		Group C		Total
		Lean	Obese	Lean	Obese	Lean	Obese	
	Low (%)	0	50	0	0	33,3	46,2	23,4
	High (%)	100	50	100	100	66,7	53,8	76,6
	Total	100	100	100	100	100	100	100

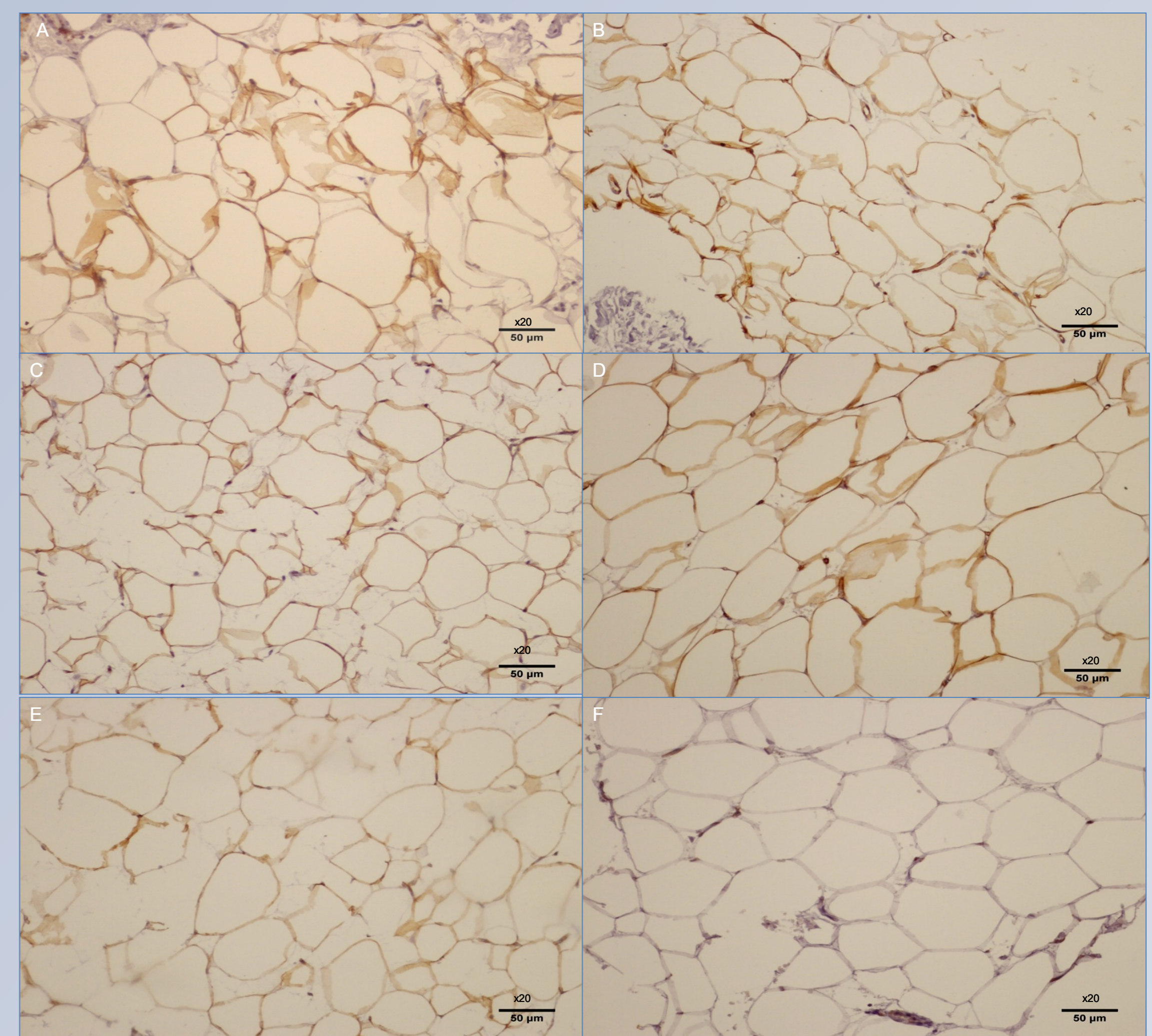


Figure 3. UCP1 in lean and obese children of Group A (A & B), Group B (C & D) and Group C (E & F). (UCP1 positive staining = brown)

■ The children with high UCP1 intensity though, exhibited a higher adipocyte number (107.33 ± 35.02 vs 83.0 ± 17.93, p=0.011). (Figure 3)

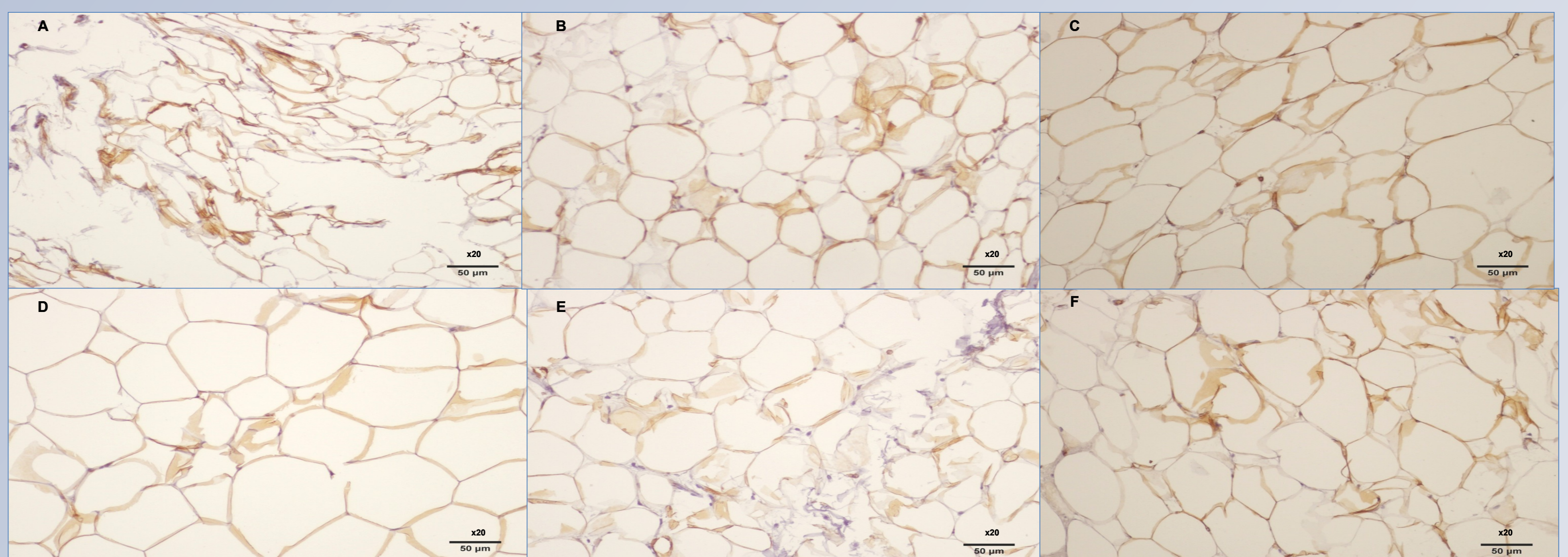


Figure 4. Children with high UCP1 intensity & higher adipocyte number (A-C) and children with low UCP1 intensity & lower adipocyte number (D-F). (UCP1 positive staining = brown)

Conclusions

1. The expression of UCP1 in typical white adipocytes in the children and adolescents may reflect a transitional stage of browning recently observed in young sheep studies².
2. UCP1 expression during childhood may contribute towards increased metabolic rate and decreased adipocyte size in an attempt to protect against the development of metabolic disorders.
3. The decreased distribution of UCP1 positive adipocytes in the adolescents may reflect the loss of browning with age and puberty that may impair further the metabolism of obese adolescents.

References

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