Anti-inflammatory dietary intervention selectively improves insulin sensitivity in metabolically unhealthy overweight and obese adolescents

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Introduction

- Anti-inflammatory nutritional approaches may attenuate obesity-induced insulin resistance
- However, results from clinical studies are not consistent, warranting increased focus on determinants of inter-subject variability, particularly within young cohorts at high-risk
- Personalised nutrition approaches suggest that pre-intervention metabotype may discriminate responders from non-responders

Aim

To investigate the effect of an anti-inflammatory dietary supplement on the metabolic phenotype of overweight and obese adolescents

✓ **Objective 1:** To examine the effect of supplementation on plasma adiponectin, an early biochemical marker of type 2 diabetes risk

✓ **Objective 2:** To assess the predictors of responsiveness to dietary intervention

Materials & Methods

- 58 adolescents (13-18 yrs) were recruited onto a double blinded, placebo-controlled, cross over intervention, and randomized to receive either the active anti-inflammatory or placebo supplement for a period of 8 weeks
- Nutritional supplementation contained: EPA and DHA (2000mg), vitamin C (567mg), α-tocopherol (390mg), green tea extract (416mg) and lycopene (16.5mg)
- Anthropometric and biochemical parameters were assessed pre and post intervention

Results

1. Anti-inflammatory supplementation increased HMW adiponectin despite no change in BMI or fat mass

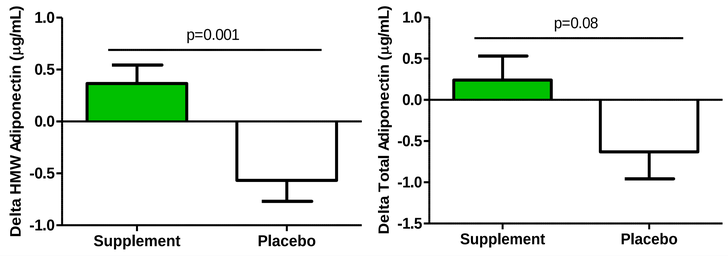

Figure 1: Change in high molecular weight (HMW) adiponectin and total adiponectin concentrations from baseline following anti-inflammatory (8 weeks) and placebo (8 weeks) interventions in overweight and obese adolescents (n=58). P-value assessed by paired samples t-test of delta values; <0.05 considered significant.

	Supplement		Placebo		
	Pre	Post	Pre	Post	P value
Weight (kg)	92.78 (22.83)	92.60 (23.00)	92.77 (22.78)	92.63 (22.22)	0.94
Body Mass Index (kg/m^2)	31.83 (6.51)	31.61 (6.56)	31.83 (6.58)	31.62 (6.28)	0.95
Body Mass Index Z-Score	2.56 (0.84)	2.53 (0.85)	2.55 (0.81)	2.53 (0.83)	0.71
Waist Circumference (cm)	105.00 (14.11)	103.89 (14.63)	104.95 (14.39)	103.78 (14.17)	0.31
Fat Mass (kg)	35.46 (16.09)	34.77 (15.62)	35.57 (16.72)	35.16 (15.99)	0.72
Glucose (mmol/L)	5.19 (0.38)	5.15 (0.40)	5.20 (0.41)	5.20 (0.36)	0.48
Insulin (mU/L)	11.59 (6.72)	10.89 (5.77)	11.50 (7.07)	10.84 (5.39)	0.98
HOMA-IR	2.72 (1.67)	2.54 (1.49)	2.70 (1.82)	2.52 (1.34)	0.97
QUICKI	0.34 (0.03)	0.34 (0.02)	0.34 (0.02)	0.34 (0.02)	0.81
TAG (mmol/L)	0.97 (0.47)	0.95 (0.47)	0.99 (0.40)	1.00 (0.47)	0.59
Total Cholesterol (mmol/L)	3.80 (0.71)	3.88 (0.66)	3.89 (0.70)	3.78 (0.65)	0.04
HDL Cholesterol (mmol/L)	1.22 (0.28)	1.23 (0.28)	1.25 (0.31)	1.19 (0.25)	0.02
LDL Cholesterol (mmol/L)	2.14 (0.53)	2.22 (0.50)	2.19 (0.55)	2.13 (0.51)	0.02
LDL:HDL	1.84 (0.55)	1.89 (0.57)	1.88 (0.83)	1.87 (0.68)	0.51
APO A1 (mg/dL)	111 (18)	109.19 (19.33)	115 (20)	111 (16)	0.37
Total Adiponectin (µg/ml)	7.56 (3.96)	7.80 (4.60)	8.26 (4.73)	7.63 (3.67)	0.08
HMW Adiponectin (µg/ml)	3.77 (2.98)	4.14 (3.35)	3.82 (2.78)	3.25 (2.32)	0.001
CD163 (ng/ml)	690.06 (303.49)	701.57 (314.40)	693.76 (297.34)	648.14 (283.70)	0.29
Complement C3 (mg/ml)	0.57 (0.31)	0.51 (0.29)	0.63 (0.44)	0.65 (0.44)	0.16
Serum TNF-α (pg/ml)	10.45(1.34)	10.76 (1.61)	10.44 (1.22)	11.03 (1.38)	0.24
Serum IL-6 (pg/ml)	2.39 (0.91)	2.50 (0.88)	2.42 (0.68)	2.50 (1.02)	0.47
PBMC TNF-α unstimulated (pg/ml)	41.74 (127.48)	24.88 (101.29)	23.00 (99.94)	12.86 (17.78)	0.25
PBMC TNF-α LPS stimulated (pg/ml)	291.31 (198.75)	286.41 (217.87)	345.74 (424.99)	331.99 (384.46)	0.43
PBMC IL-6 unstimulated (pg/ml)	120.08 (216.82)	94.2 (200.69)	70.16 (123.96)	83.20 (178.16)	0.76
PBMC IL-6 LPS stimulated (pg/ml)	1.1x10^4 (0.8x10^4)	1.0x10^4 (0.7x10^4)	1.1x10^4 (0.8x10^4)	1.1x10^4 (0.7x10^4)	0.82

Table 1: Anthropometric, metabolic and inflammatory characteristics pre and post ant-inflammatory nutritional supplement in overweight and obese adolescents (n=58). P-value assessed by paired samples t-test of delta values; <0.05 considered significant.

2. HOMA-IR significantly improved in response to anti-inflammatory supplement in a sub cohort

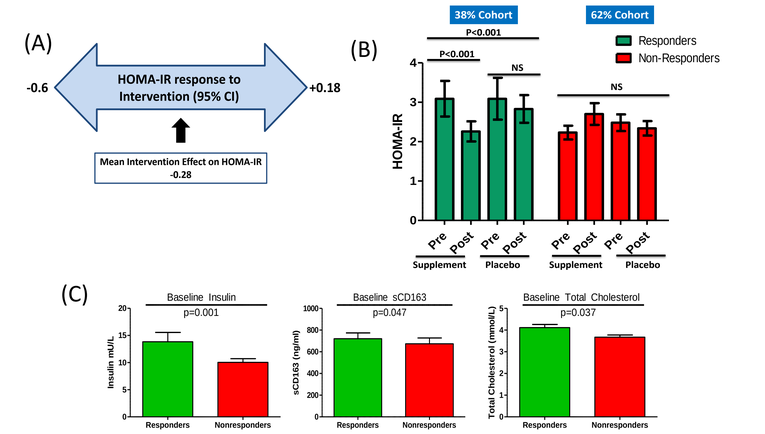

Figure 2: A) Responders were classified by a -0.28 unit improvement in HOMA-IR[1] B) 38% of the cohort demonstrated a favourable response to intervention. No significant difference in HOMA-IR was detected in non-responders. P-value as assessed by repeated measures ANOVA; <0.05 considered significant; C) Characteristics that significantly differed between responders versus nonresponders at baseline. P-value assessed as independent samples t-test; <0.05 considered significant.

3. mRNA expression of adiponectin receptors was modulated post supplementation

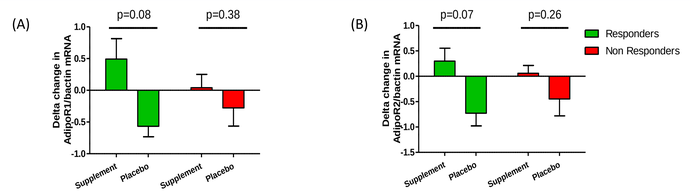

Figure 3: RNA was isolated from PBMCs obtained from responders and non-responders and gene expression was quantified by real time PCR. (A) AdipoR1, (B) AdipoR2 levels increased in those who responded favorably to the intervention (n=9-10/group). P-value assessed by paired samples t-test of delta values.

4. Baseline HOMA-IR, soluble CD163 and LDL:HDL ratio explained variance in HOMA-IR response to anti-inflammatory supplementation

$R^{2=}0.673, p<0.001$

Variable	β	p
Baseline HOMA-IR	-0.597	0.001
Delta CD163	0.468	<0.001
Baseline LDL:HDL	0.342	0.003
Baseline CD163	0.250	0.025
Delta Adiponectin	-0.222	0.035

Table 2: Stepwise multiple linear regression analysis of factors determining intervention response. Baseline HOMA-IR, sCD163 and LDL:HDL ratio as well as delta sCD163 and delta total adiponectin explained 67.3% of the variance in HOMA-IR response to anti-inflammatory supplementation.

Reference 1: Love-Osborne et al (2008) J. Pediatr 152(6):817-22

Conclusions

✓ Anti-inflammatory nutrient supplementation improved HMW adiponectin biology – adiponectin is an abundantly expressed adipokine with potent insulin sensitising effects and is an important biomarker of future risk of metabolic sequalae

✓ Evidence for selective improvement in insulin resistance

✓ Despite similar BMI, those with an adverse phenotype - 'metabolically unhealthy obesity'- responded more favourably to anti-inflammatory supplementation

✓ Baseline phenotype as well as delta sCD163 and delta total adiponectin significantly predicted HOMA-IR response

This research was funded by The National Children's Research Centre, Crumlin Hospital, Ireland. HMR & FCM are supported by Science Foundation Ireland Principal Investigator Programme (11/PI/1119) and Wellcome Trust Career Development Fellowship (097311/Z/11/1) respectively. This trial was registered at clinicaltrials.gov as NCT01665742. We wish to acknowledge Smartfish, Oslo and Best Formulations, California for provision of the anti-inflammatory and placebo supplementation.

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