Reductions in plasma endocannabinoids following bariatric surgery in morbidly obese females with impaired glucose homeostasis: A non-randomized prospective study

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Introduction

- Endocannabinoids (ECs) are bioactive lipid mediators
  - N-arachidonyl ethanolamine (AEA)
  - N-palmitoyl ethanolamine (PEA)
  - N-oleoyl ethanolamine (OEA)
  - related N-acylethanolamine (NAE) derivatives
  - 2-arachidonyl glycerol (2-AG)
- Endocannabinoid system (ECS) plays a critical role in regulation of body weight and may have a role in aetiopathogenesis of Type 2 Diabetes (T2DM)
- Elevated circulating levels of AEA and 2-AG in obese people compared to non-obese controls of both genders
- Little information available on the effects of extreme weight loss associated with bariatric surgery in relation to the ECS

Aims

- To examine gender differences and changes in circulating ECs in relation to bariatric surgery
- To examine the association between circulating ECs and markers of obesity, and insulin and glucose homeostasis pre- and post-bariatric surgery

Methods

- Non-randomised prospective study
- 20 participants undergoing bariatric surgery
- All participants either had T2DM, or impaired glucose regulation
- Fasting and 2-hour plasma glucose, lipids, insulin, C-peptide, measures of insulin sensitivity and plasma ECs were measured pre-operatively and 6 months post-operatively

Results

Whole group analysis (Table 1)

- Significant reduction in weight, HbA1c, 2- hour plasma glucose, and fasting insulin, and increase in hepatic insulin clearance at 6 months
- No significant changes in the AEA, OEA, PEA and 2-AG post-operatively

Gender-specific analysis (Table 2)

- Differences in AEA, OEA and PEA between males and females pre-operatively
- Reductions in AEA & PEA in females post-operatively

Correlations between circulating ECs and markers of obesity, insulin and glucose homeostasis pre and post-operatively (Table 3)

Table 1: Pre and post-operative clinical and biochemical measurements

Measurement	Preoperative (n=20)	Postoperative (n=20)	P
Weight (kg)	160.2 (44.2)	124.8 (29.4)	<0.001
BMI (kg/m^2)	57.3 (14.1)	45.4 (10.1)	<0.001
HbA_{1c} (%)	7.2 (1.5)	6.1 (1.3)	0.02
FPG (mmol/L)	7.8 (3.3)	6.0 (3.1)	0.13
2-hr PG (mmol/L)	12.7 (4.9)	8.3 (5.9)	0.01
Fasting insulin (IU/mL)	27.9 (16.2)	11.4 (6.7)	0.002
Fasting C-peptide (ng/mL)	3.6 (1.5)	2.9 (1.5)	0.10
HOMA %S	305.8 (208.3)	617.5 (492.5)	0.03
HOMA- IR	0.4667 (0.3016)	0.3600 (0.4154)	0.32
C-pep: Insulin ratio	0.1744 (0.0996)	0.2741 (0.1246)	0.001
AEA (pmol/mL)*	0.21 (0.04)	0.19 (0.04)	0.33
OEA (pmol/mL)*	1.05 (0.13)	0.93 (0.18)	0.25
PEA (pmol/mL)*	0.83 (0.09)	0.74 (0.09)	0.10
2-AG (pmol/mL)*	5.0 (1.55)	4.2 (1.40)	0.14

* Geometric mean and approximate standard deviation shown for log transformed data

Table 2: Pre and post-operative gender differences in ECs

Measurement	Preoperative			Postoperative		
	Females	Males	P	Females	Males	P
AEA (pmol/mL)*	0.297 (0.042)	0.147 (0.021)	<0.001	0.209 (0.049)†	0.165 (0.033)	0.30
OEA (pmol/mL)*	1.263 (0.125)	0.869 (0.085)	0.002	0.947 (0.232)	0.912 (0.127)	0.86
PEA (pmol/mL)*	0.964 (0.096)	0.720 (0.054)	0.005	0.759 (0.110) ††	0.713 (0.084)	0.67
2-AG (pmol/mL)*	5.163 (1.831)	4.019 (2.184)	0.43	5.156 (2.086)	3.249 (0.840)	0.51

*Geometric and approx SD shown. Log transformed.
†P=0.02, Preoperative v 6 months postoperatively ††P=0.007, Preoperative v 6 months postoperatively

Table 3: Correlations between ECs and markers of obesity, and insulin and glucose homeostasis

Variable	AEA	OEA	PEA	2-AG
Weight				
0 month	0.10 (0.68)	**0.49 (0.03)**	0.36 (0.12)	0.20 (0.45)
6 months	0.01 (0.96)	0.01 (0.97)	-0.23 (0.35)	-0.16 (0.53)
Waist				
0 month	0.10 (0.68)	**0.52 (0.02)**	0.40 (0.08)	0.26 (0.33)
6 months	-0.13 (0.62)	-0.04 (0.86)	-0.28 (0.25)	0.11 (0.70)
Fasting glucose				
0 month	0.15 (0.55)	0.05 (0.84)	0.09 (0.71)	**-0.59 (0.04)**
6 months	0.54 (0.05)	0.11 (0.62)	0.18 (0.46)	-0.09 (0.75)
2-hour glucose				
0 month	**0.55 (0.01)**	0.11 (0.65)	0.17 (0.47)	0.003 (1.00)
6 months	-0.02 (0.94)	-0.24 (0.33)	-0.13 (0.60)	-0.42 (0.10)
Fasting insulin				
1 month	0.28 (0.26)	**0.49 (0.04)**	**0.49 (0.04)**	0.18 (0.54)
6 months	-0.03 (0.89)	0.06 (0.81)	0.08 (0.76)	-0.19 (0.49)
HOMA S%				
1 month	**-0.71 (0.002)**	-0.34 (0.18)	-0.47 (0.06)	0.16 (0.57)
6 months	-0.35 (0.16)	-0.25 (0.33)	-0.33 (0.18)	-0.21 (0.44)
HOMA- IR				
0 month	**0.61 (0.009)**	**0.48 (0.05)**	**0.53 (0.03)**	0.27 (0.32)
6 months	0.40 (0.1)	0.28 (0.27)	0.25 (0.31)	0.38 (0.15)
Systolic BP				
0 month	**0.40 (0.09)**	0.11 (0.66)	0.25 (0.30)	-0.01(1.0)
6 month	-0.13 (0.61)	-0.27 (0.26)	-0.06 (0.81)	-0.07 (0.78)
Diastolic BP				
0 month	**0.48 (0.04)**	0.01 (0.96)	0.14 (0.56)	**-0.52 (0.04)**
6 months	-0.06 (0.83)	-0.08 (0.76)	0.08 (0.74)	-0.23 (0.38)
LDL-C				
0 month	0.15 (0.54)	0.15 (0.52)	**0.44 (0.04)**	-0.02 (0.94)
6 months	-0.27 (0.27)	-0.26 (0.28)	-0.04 (0.87)	0.13 (0.62)
HDL-C				
0 month	-0.21 (0.37)	-0.12 (0.53)	-0.31 (0.18)	**-0.73 (0.001)**
6 months	-0.32 (0.18)	0.18 (0.45)	0.28 (0.25)	0.03 (0.91)
2-AG				
0 month	0.08 (0.76)			
6 months	-0.01 (0.98)			
OEA				
0 month	**0.52 (0.02)**			
6 months	**0.60 (0.005)**			
PEA				
0 month	**0.71 (<0.001)**			
6 months	**0.61 (0.005)**			

r-values with the P-values in brackets. Significant correlations in bold.

Conclusions

- Gender differences exist in circulating levels of ECs in morbidly obese subjects
- Specific correlations exist between different ECs and markers of obesity, and insulin and glucose homeostasis pre-operatively

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