Macrophage polarization in patients with obese diabetes and its potential role as a predictive marker of diabetic improvement after bariatric surgery

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CONFLICT OF INTEREST DISCLOSURE

[ ] I have no potential conflict of interest to report

[O] I have the following potential conflict(s) of interest to report:

- Type of affiliation / financial interest: none
- Receipt of grants/research supports: Olympus, JW Pharmaceutical, Abbott
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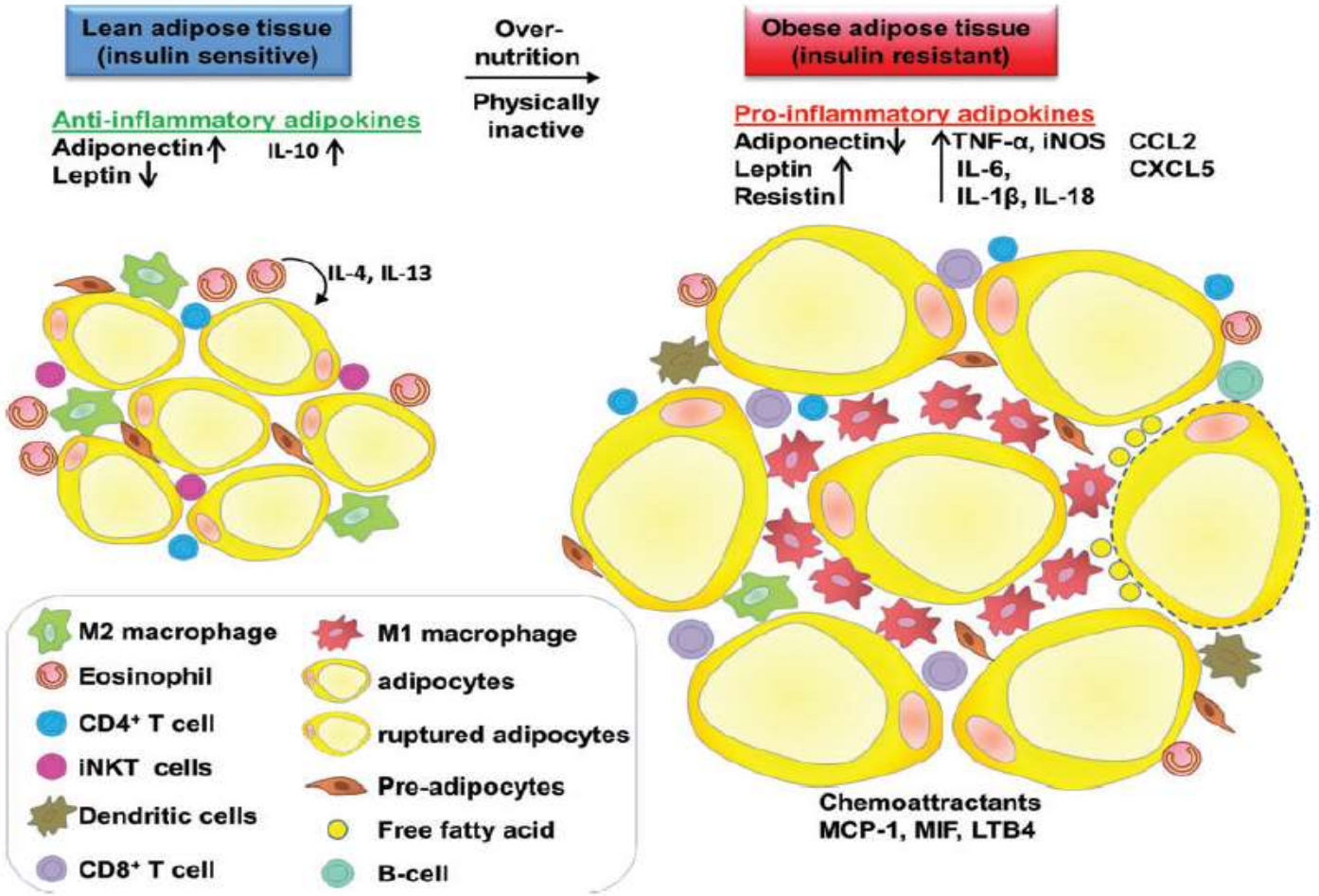
- Other support (please specify): none

Background (1)

Inflammation in adipocyte in type II DM



Chronic inflammation

↓

insulin resistance ↑

↓

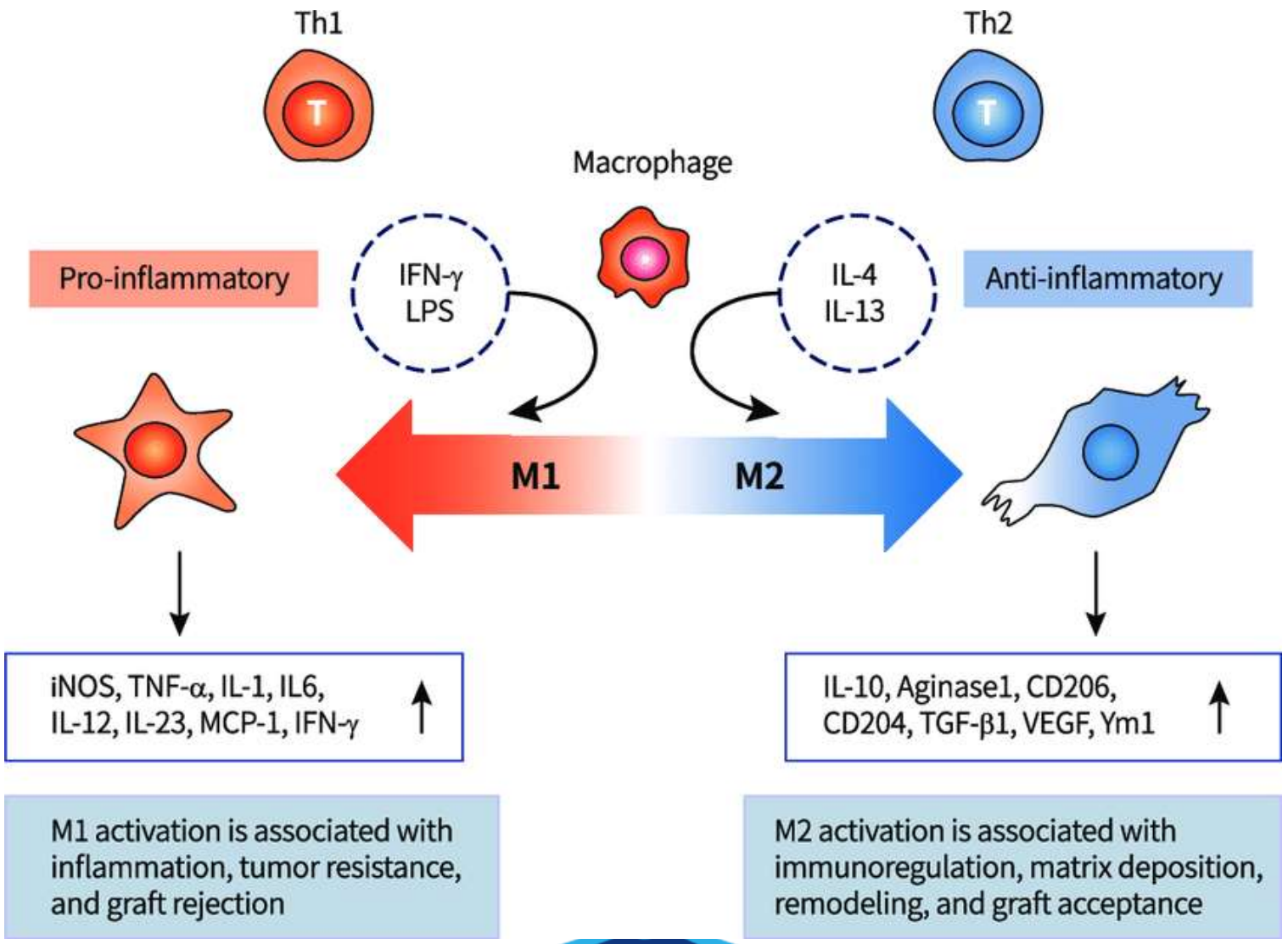
Type II DM

Appari M, et al. Antioxid Redox Signal 2018

Background (2)

M1 macrophage polarization (M1/M2 ↑) in obesity

M1



M2

Purpose

- ✓ To analyze the **adipocyte inflammation** and **M1/M2 ratio** in visceral fat according to the presence of obesity and diabetes

- ✓ To explore the possibility of **preoperative M1/M2 ratio** (Mϕ polarization) as a predictor for **DM improvement** after bariatric surgery

Methods (1) Patients

- **Patient Collection**

(1) Prospective study with informed consent (SNUH IRB ; 1909-061-1064)

(2) From 2019.11 to 2022.03 at Seoul National University Hospital (SNUH)

(3) Morbid obesity group : patients with bariatric surgery patients with BMI ≥ 30kg/m^2

(4) Non-obese group : patients with early gastric cancer (EGC) patients with BMI < 25kg/m^2

- **Grouping (n=20 in each group)**

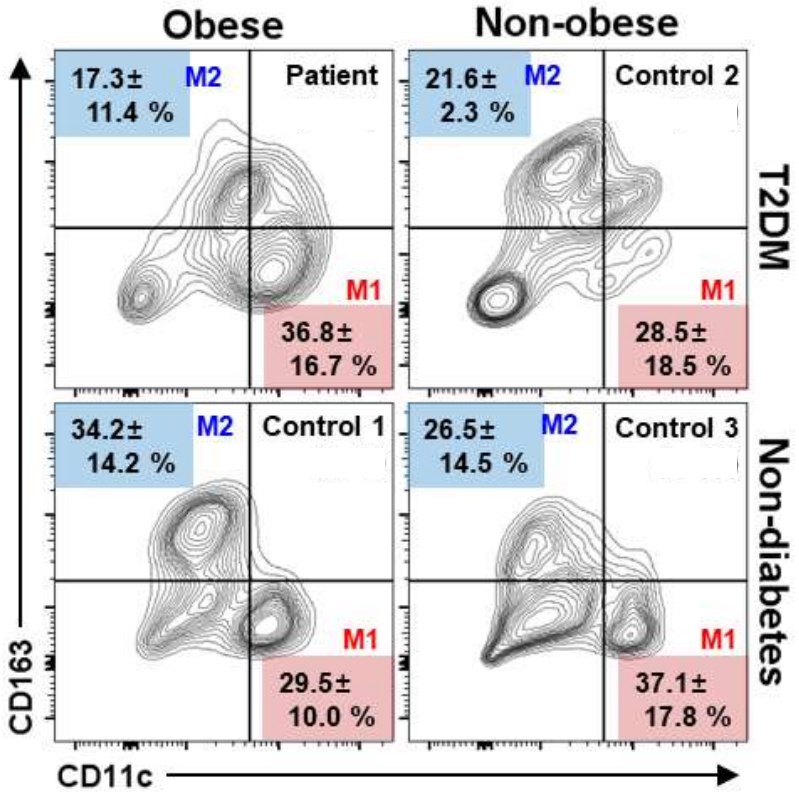
Obesity / Diabetes	**Morbid obesity (BMI ≥ 30)**	**Non-obese (BMI < 25)**
DM (+)	Experimental	Control 2
DM (-)	Control 1	Control 3

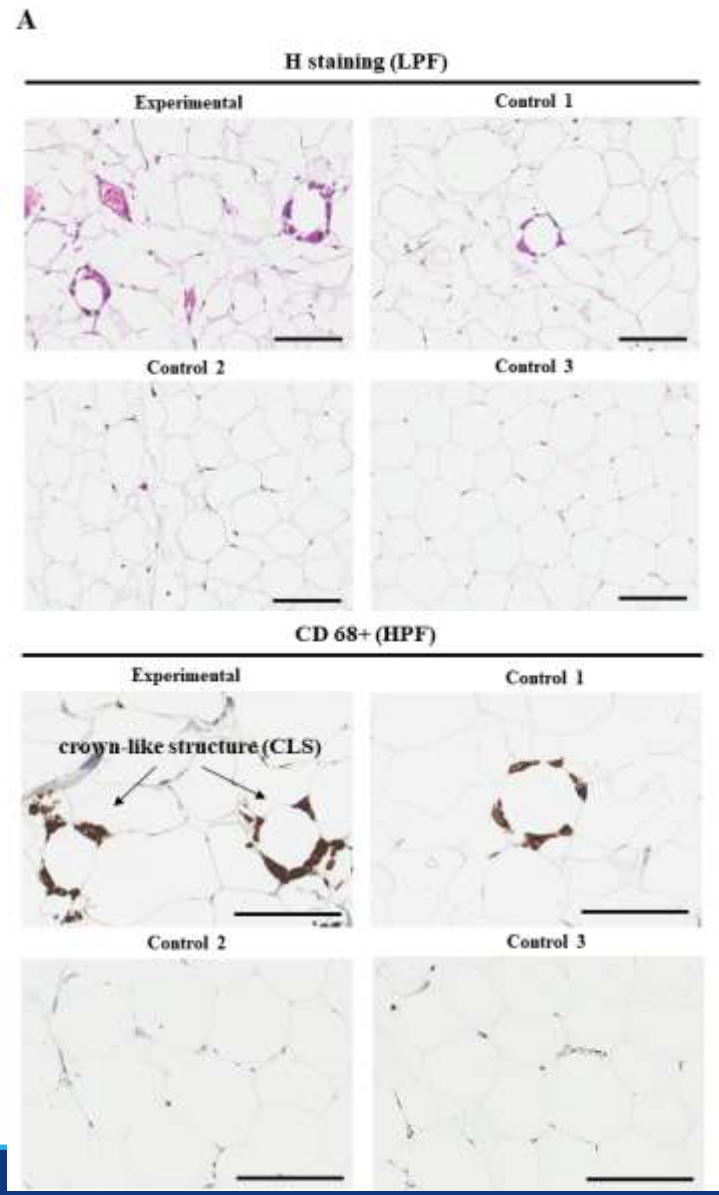
Methods (2)

Visceral adipose tissue (omentum)

1. Visceral adipose tissue (greater omentum obtained during the surgery)

- Flow cytometry ; macrophage proportion (M1/M2 ratio)
- qPCR ; pro-inflammatory (M1: **PELI1, NOS2**) & anti-inflammatory gene (M2: **ARG1**)
- IHC ; crown-like structures (CLS) count, macrophage count





Methods (3)

Clinical Data

1. Visceral adipose tissue (greater omentum obtained during the surgery)

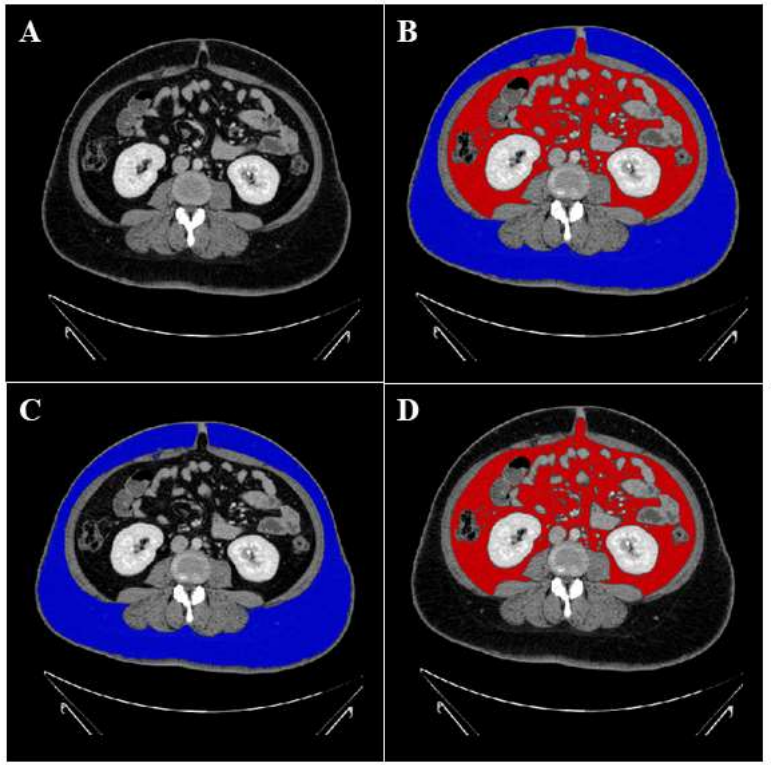
- Flow cytometry ; macrophage proportion, M1/M2 polarization
- PCR ; proinflammatory (M1: PELI1, NOS2) & anti-inflammatory gene (M2: ARG1)
- IHC ; crown-like structures (CLS) count, macrophage count

2. Blood samples (preop)

- inflammation indices ; CBC, CRP
- DM lab ; fasting glucose, HbA1c, insulin, c-peptide

3. CT volumetry (preop) : visceral & subcutaneous fat ratio

4. Clinical parameter : ABCD score, IMS score, DiaRem/Ad-DiaRem score



FOLLOW-UP

- Postop 3 weeks, 3 mo, 6 mo, 12 months
- DM remission/improvement

Results (1)

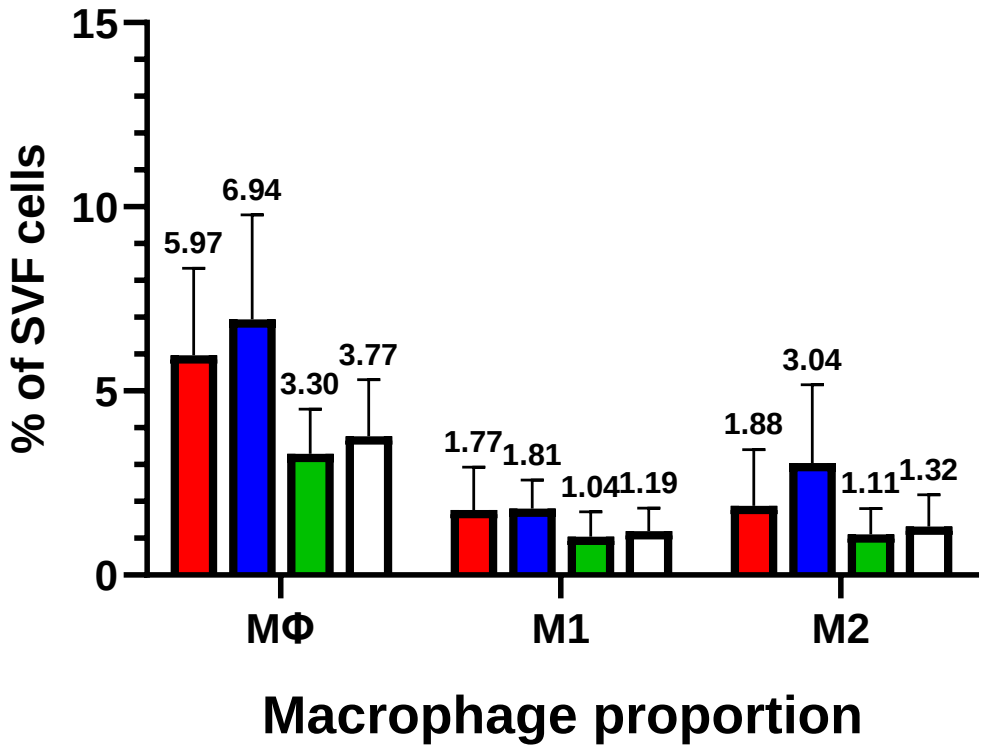
Demographics & DM lab

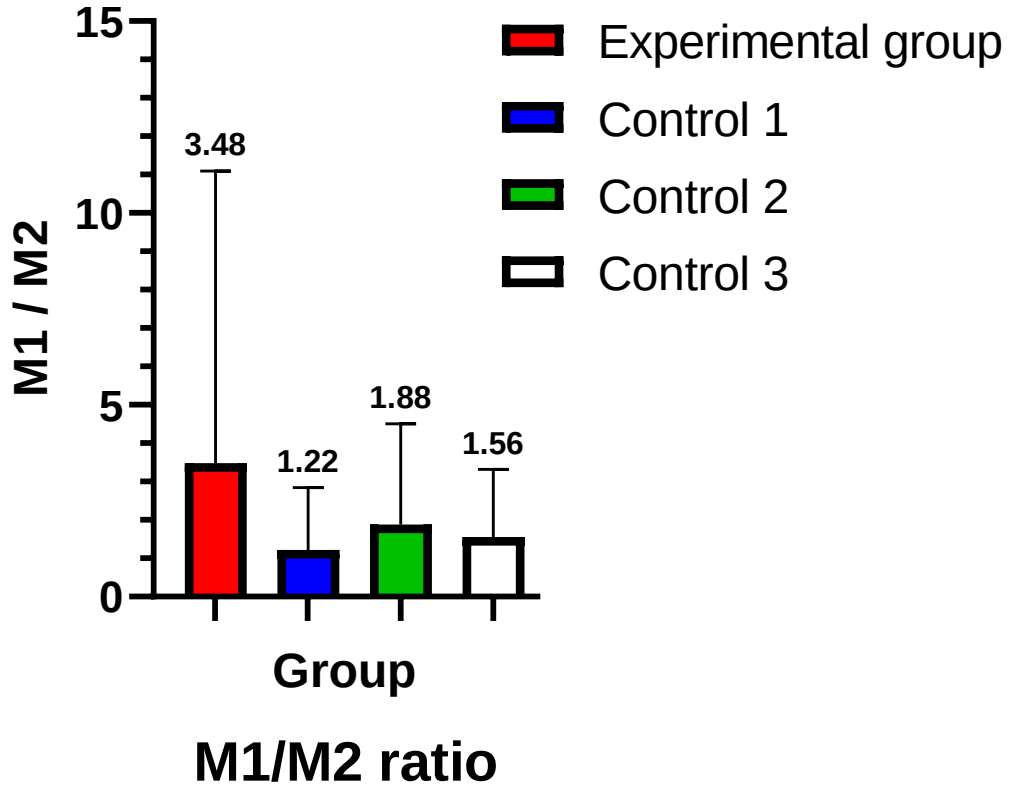
Characteristics (n=81)		Experimental (N = 20)	Control 1 (N=20)	Control 2 (N=20)	Control 3 (N=21)
Age (year ± SD)		39.45±11.99	32.70±10.82	69.55±5.91	57.86±9.35
Sex	Male (%)	10 (50.0)	6 (30.0)	15 (75.0)	9 (42.9)
	Female (%)	10 (50.0)	14 (70.0)	5 (25.0)	12 (57.1)
BMI (kg/m^2 ± SD)		40.42±5.48	39.78±5.46	22.65±1.87	23.29±2.21
Metabolic surgery type	Sleeve gastrectomy (%)	17 (85.0)	18 (90.0)		
	Gastric bypass (%)	3 (15.0)	2 (10.0)		
Fasting glucose (mg/dL)		**158.65±71.68**	99.89±16.77	**131.50±22.02**	94.76±15.12
HbA1c (%)		**8.13±1.79**	5.5±0.39	**6.99±0.46**	5.61±0.25
Fasting insulin (uIU/ml)		**20.69±12.48**	**24.85±16.75**	7.17±2.68	9.11±3.51
C-peptide (ng/ml)		**4.14±2.52**	**3.27±1.07**	1.73±1.02	1.28±0.53
HOMA-IR		**7.53±5.96**	**6.47±6.09**	2.44±1.12	2.14±0.93
V/S ratio					0.59±0.49

FBS & HbA1c ; elevated in Experimental & Control 2
Insulin, C-peptide, & HOMA-IR ; elevated in Experimental & Control 1

Results (2)

Flow cytometry

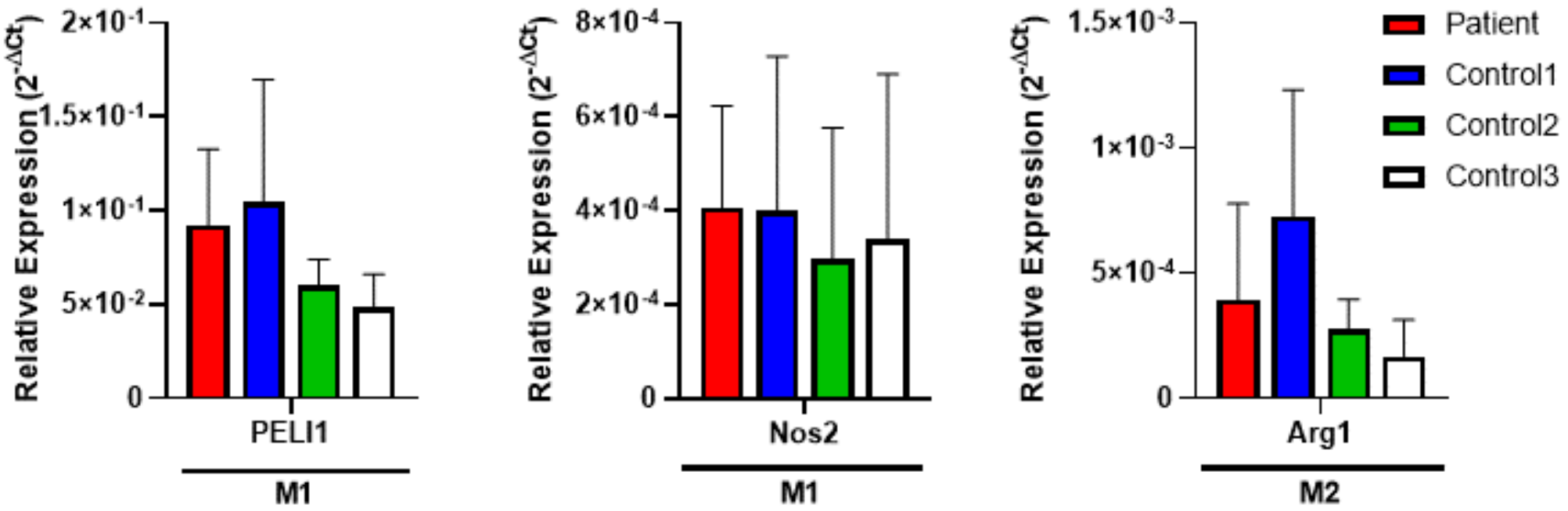




M1/M2 ratio ; increased in experimental group

Results (3)

PCR (PELI1, NOS2, ARG1)



M1/M2 ratio ; increased in experimental group

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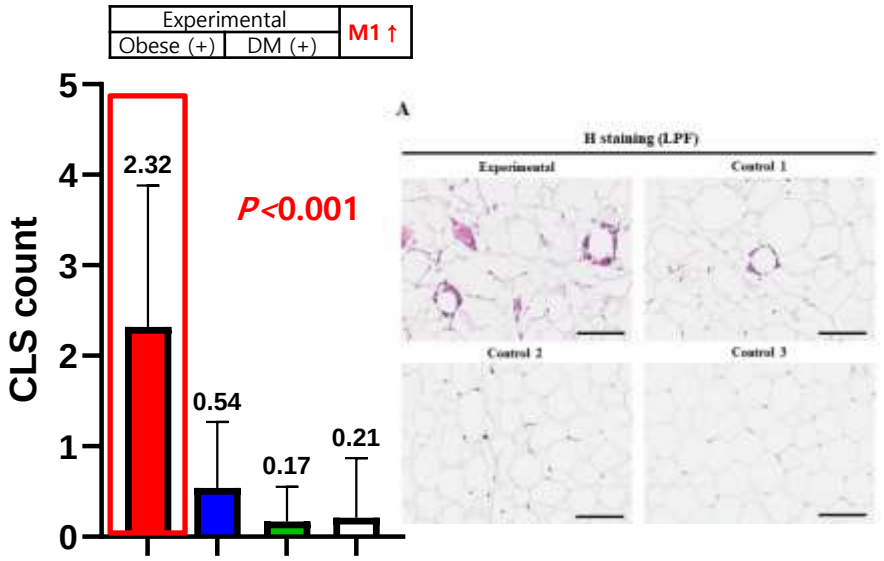
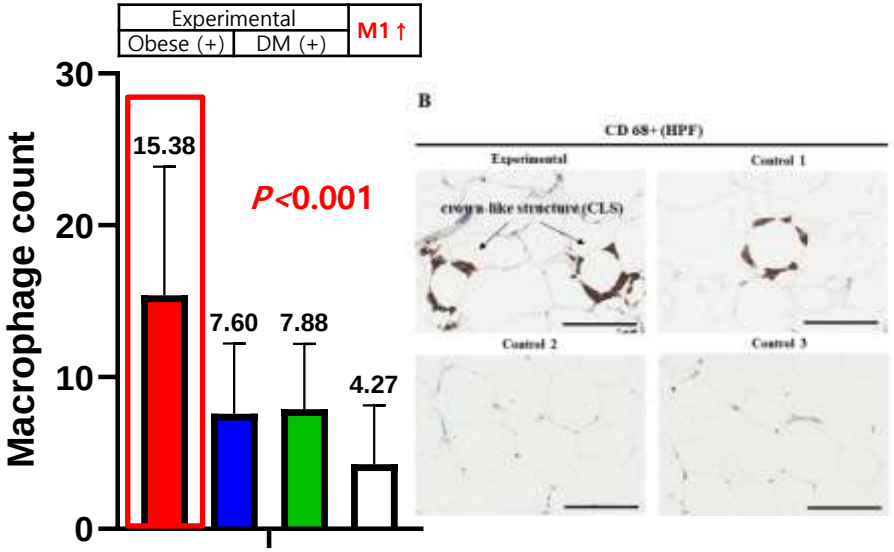
Results (4)

IHC (CLS, Mϕ)

Crown-like structure count (H&E stain)



Macrophage count (IHC, anti-CD68 Ab)



CLS & Mϕ ; increased in experimental group

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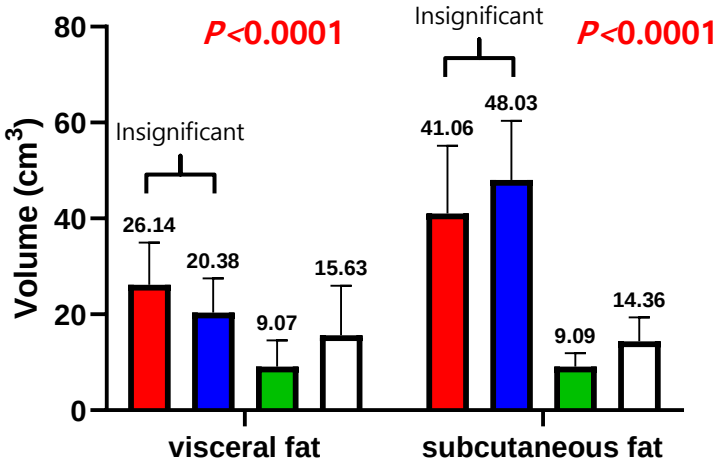
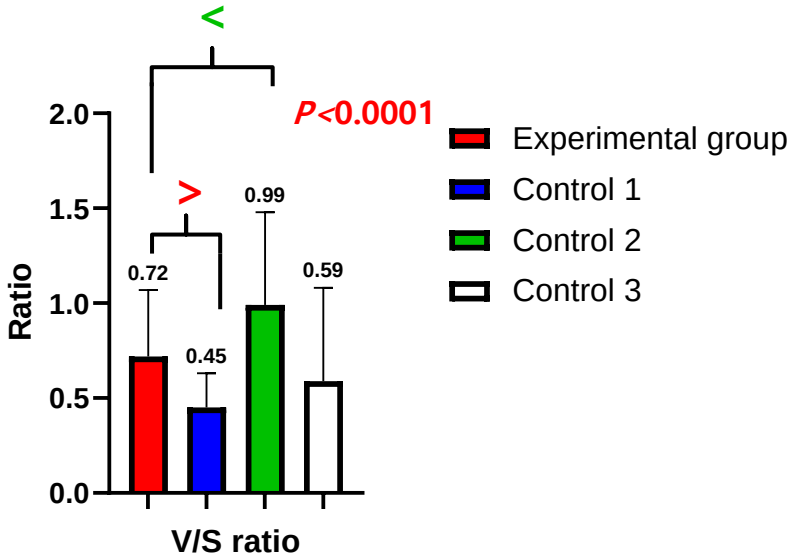
Results (5)

CT volumetry (V/S ratio)





V/S ratio; increased in experimental group

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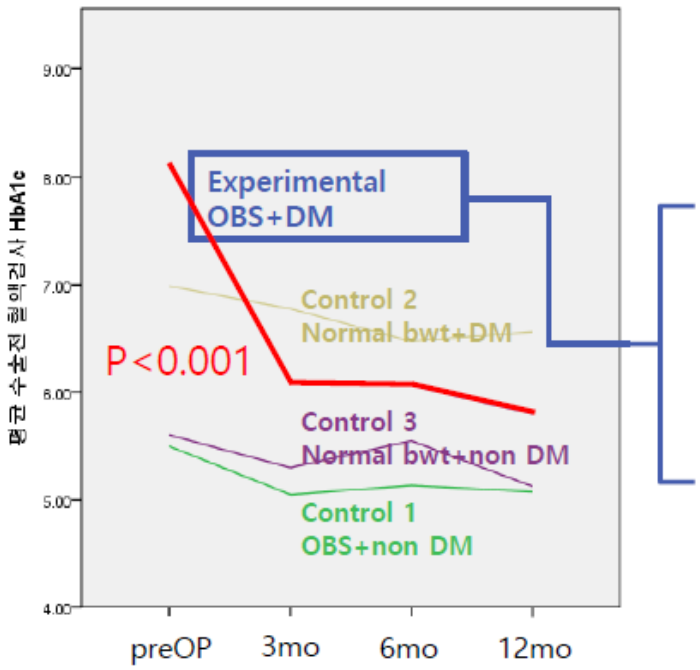
Results (6)

M1/M2 ratio & DM remission



Parameters	HbA1c reduction ratio, 3mo	HbA1c reduction ratio, 6mo	HbA1c reduction ratio, 12mo
M1	0.0037	<0.0001	0.0116
M1/M2 ratio	0.0372	0.0134	0.0344
ABCD	0.1136	0.0461	0.4514
IMS	0.3067	0.2005	0.0002
DiaRem	0.0668	0.0265	0.0105
Ad-DiaRem	0.4535	0.3540	0.0103

M1/M2 ratio ; better correlated than existing clinical prediction models

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Conclusion

1. Inflammation on adipocyte ; one of the key mechanisms for IR
2. M1/M2 ↑ (Mϕ polarization) on adipocyte

   - related to “Dead macrophage” (Crown like structure)

   - related to DM remission after bariatric surgery (more reliable than clinical models?)
3. More researches are needed to reveal the underlying mechanisms related to IR & type II DM