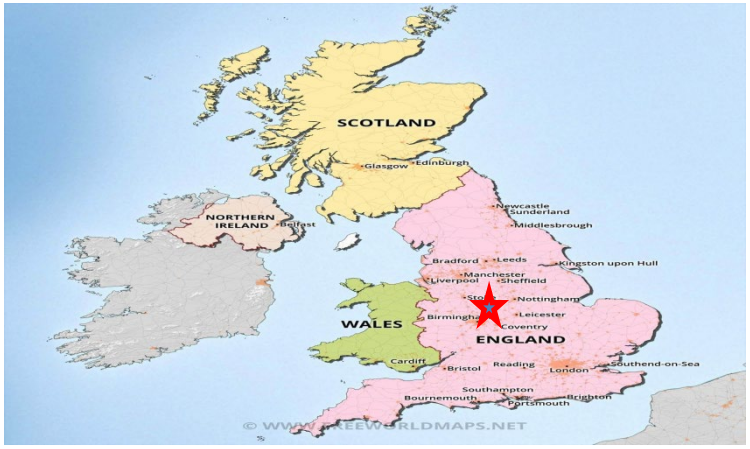
# *When and why do patients with Alstrom syndrome develop diabetes and Fatty liver disease? What can be done about it?*

Tarekegn Hiwot
Department of Endocrinology
Queen Elizabeth Hospital, Birmingham

# Birmingham


SCOTLAND
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London
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Southampton
Bournemouth
Portsmouth
Brighton

# Our Alstrom syndrome national service in Birmingham

- Centre of clinical excellence for AS
- Large number of patients with AS
- Centre of research excellence
- Strong international collaboration
- Patient and families committed to make a difference
- ASUK- determined to change the life of their members

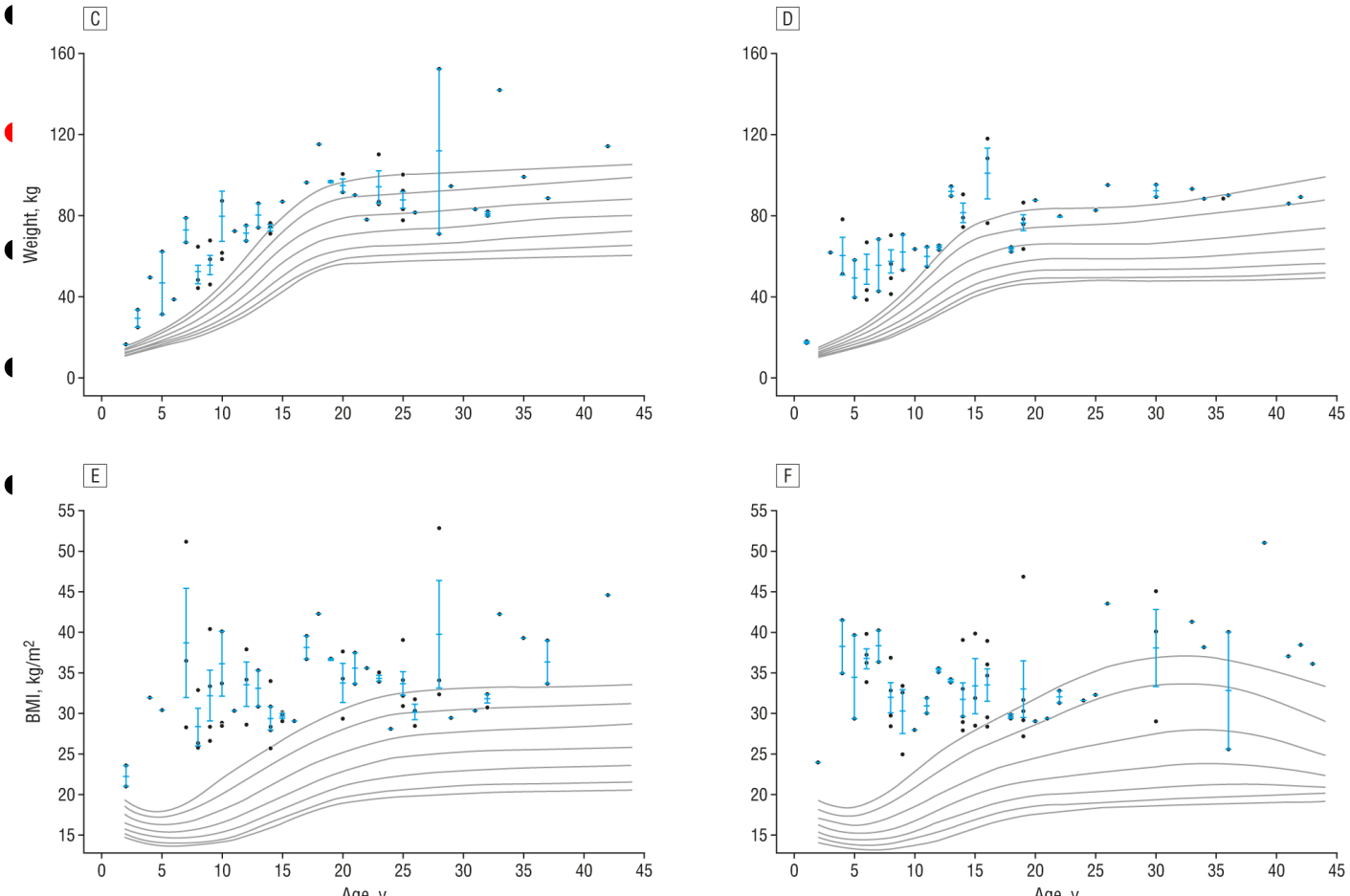
# Metabolic syndrome

- Obesity = Insulin resistance
- Obesity = diabetes, dyslipidaemia, ↑BP and NAFLD, CVD

# *Metabolic syndrome In Patients with Alstrom syndrome*

- Obesity from early childhood

n birth

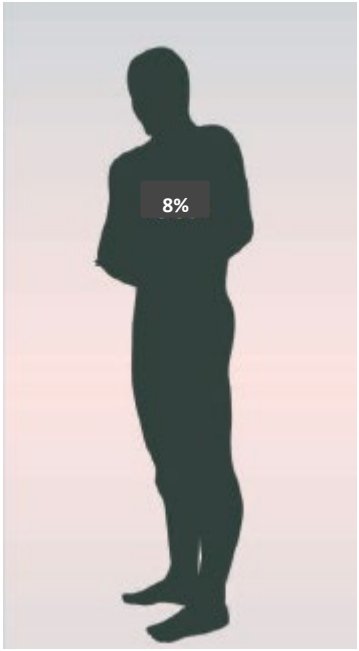


Why do patients with Alstrom syndrome suffer from extreme insulin resistance disproportionate to their weight/BMI?

**Normal BMI**
**Metabolically healthy**


- Reduced fat
- Increased muscle
- Increased fitness
- Normal insulin sensitivity
- Normal blood sugar
- Low cardiovascular risk

**Normal BMI**
**Metabolically unhealthy**

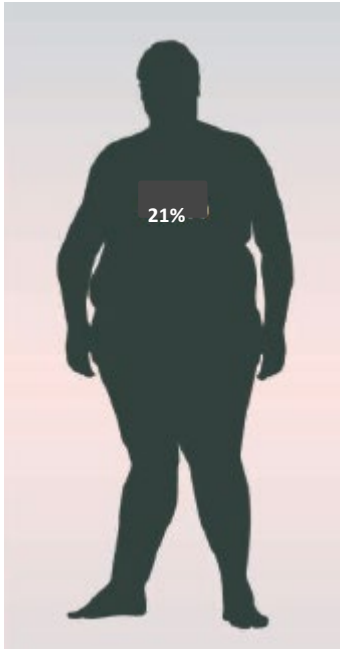



- Chronic illness
- Muscle loss (sarcopenia)
- Excess visceral fat
- Reduced fitness
- Insulin resistance
- Diabetes
- Inflammation
- High cardiovascular risk
- High cancer risk

**Obese BMI**
**Metabolically healthy**


- Excess subcutaneous > visceral fat
- Increased muscle
- Increased fitness
- Hyperinsulinemia
- Normal insulin sensitivity
- Normal blood sugar
- Mild cardiovascular risk

**Obese BMI**
**Metabolically unhealthy**

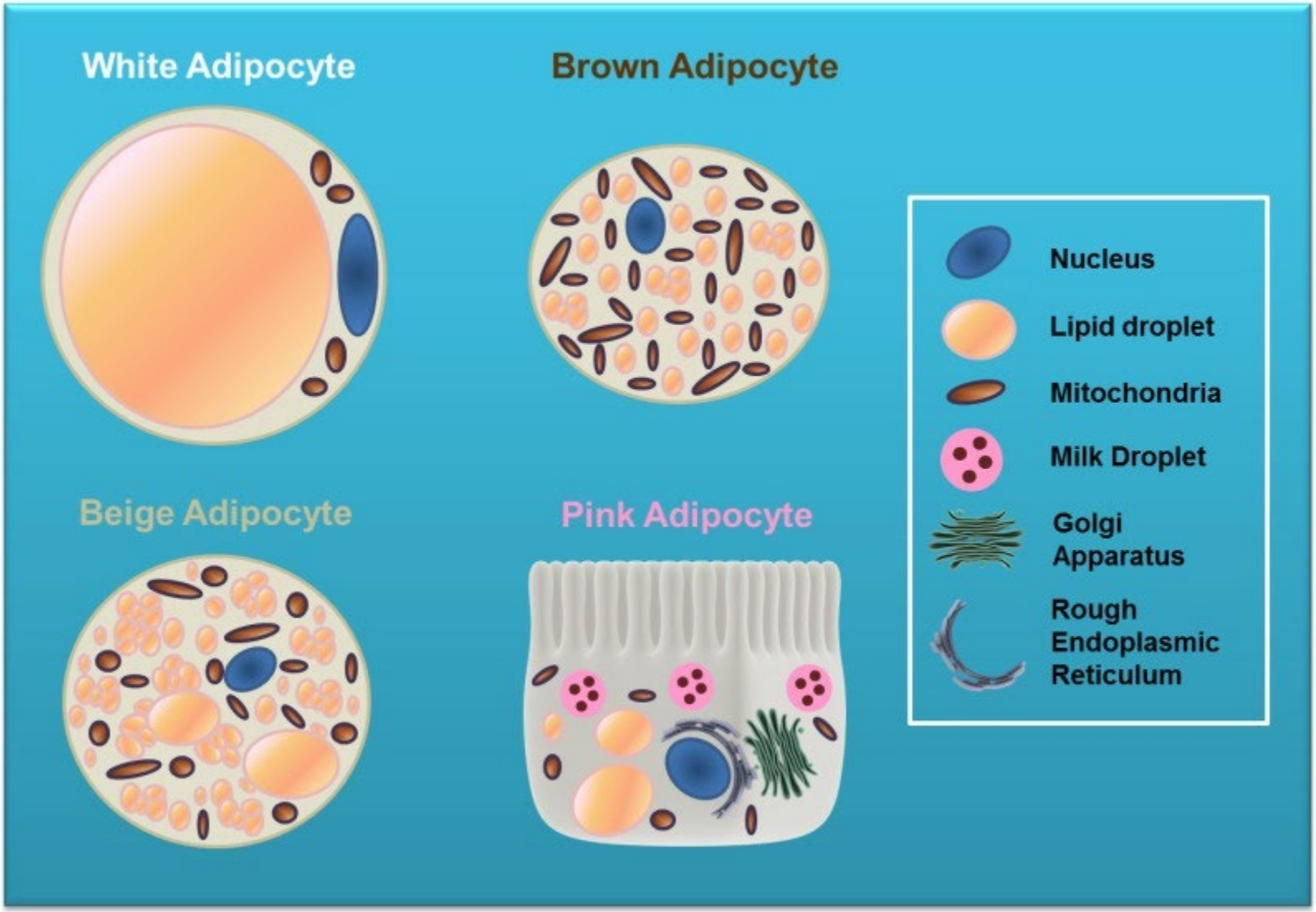



- Excess visceral > subcutaneous fat
- Muscle loss (sarcopenia)
- Reduced fitness
- Hyperinsulinemia
- Diabetes
- Dyslipidemia
- Inflammation
- High cardiovascular risk
- High cancer risk

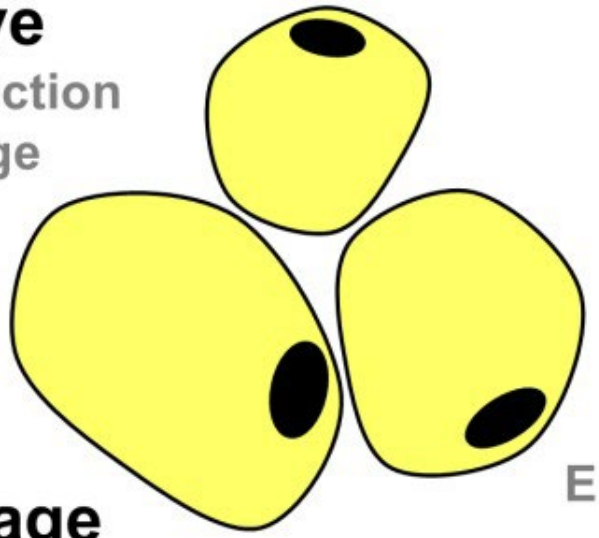
# Adipose tissue (AT)

- specialized connective tissue consisting of lipid-rich cells called adipocytes
- Constitute 20-25% healthy person's weight
- Based on location- subcutaneous (under the skin) and visceral (surrounding organs).
- Based on morphology - White /Brown/Beige/? Pink adipose tissue

# Adipocyte types are described by color hues



# Fat cell functions



**Insulin Sensitive**

Energy production and storage

**Lipid Storage**

TAG

Homeostasis between lipolysis and lipogenesis

**Secretory functions**

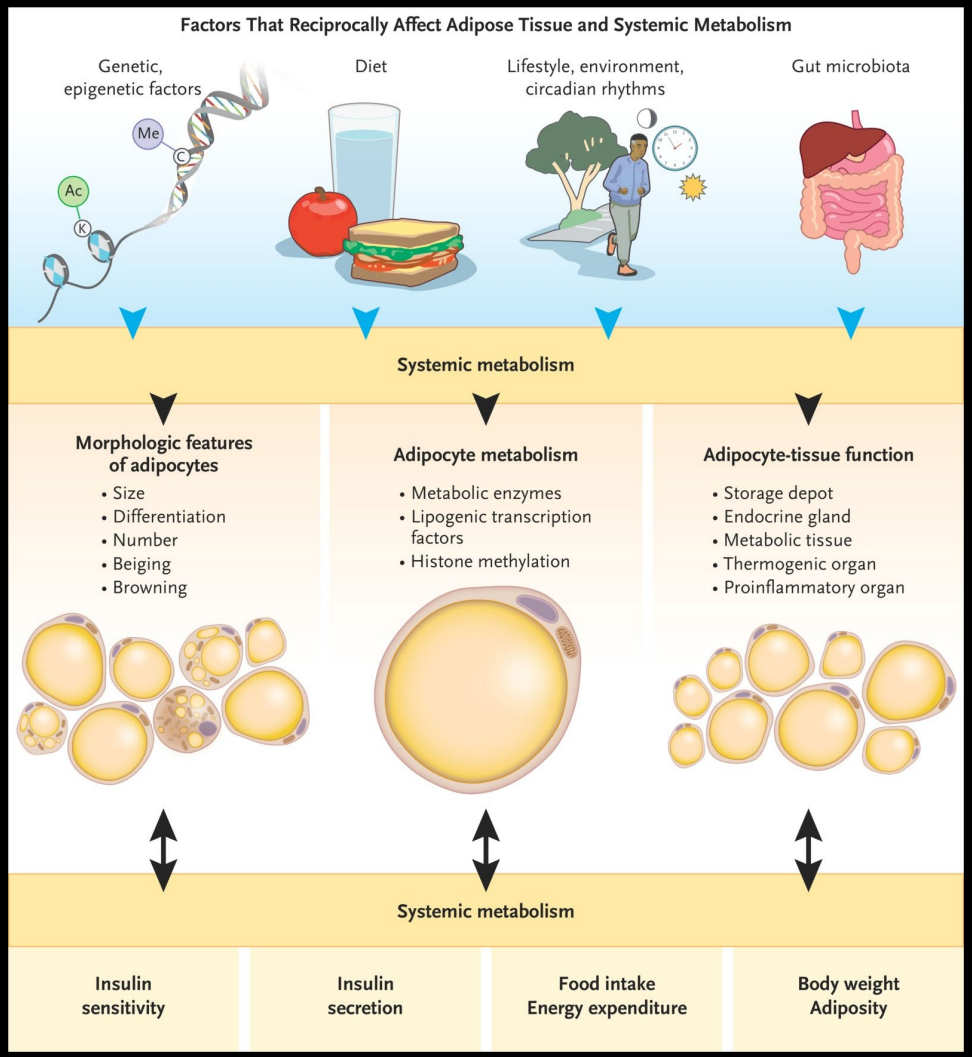
Endocrine hormones

miRNAs

Complement factors

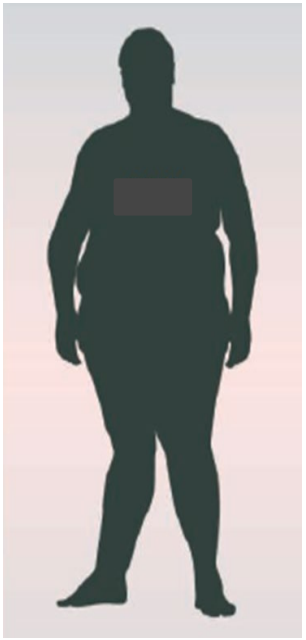
Exosomes

# Reciprocal Relationship between Function of White Adipose Tissue and Systemic Metabolism.




Santoro A, Kahn BB. N Engl J Med2023;388:2071-2085

**Overweight/obese Alstrom Syndrome (N=12)**



- Age – 26
- Male (%) – 67
- Weight (kg) – 76.32±14.5
- BMI (kg/m2) – 30.34 ±6
- Waist circumference (cm) – 96.04± 12
- Diabetes 67%
- NAFLD (83%)
- NAFLD with scar (55%)
- HDL 0.78± 0.23mmol/L

**Overweight/obese controls (N=15)**

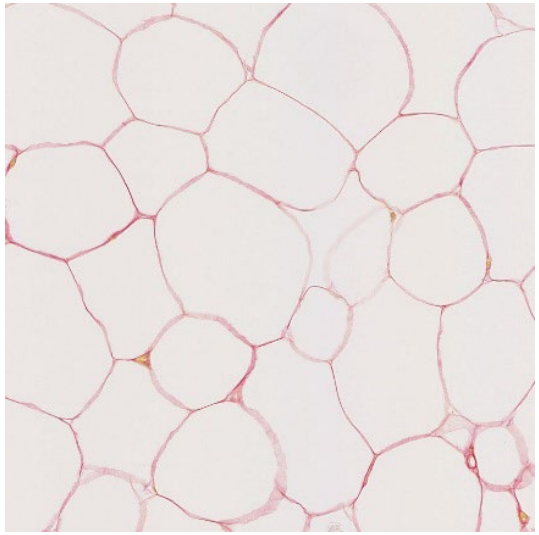
- Age – 33
- Male (%) – 60
- Weight (kg) – 93.3±22
- BMI (kg/m2) – 31.8±7
- Waist circumference (cm) – 105.7±20
- Diabetes (%) – 0
- NAFLD ( 13%)
- NAFLD with scar ( 0 %)
- HDL 1.27± 0.24mmol/L

**Extremely obese Bardet-Biedl Syndrome (N=9)**

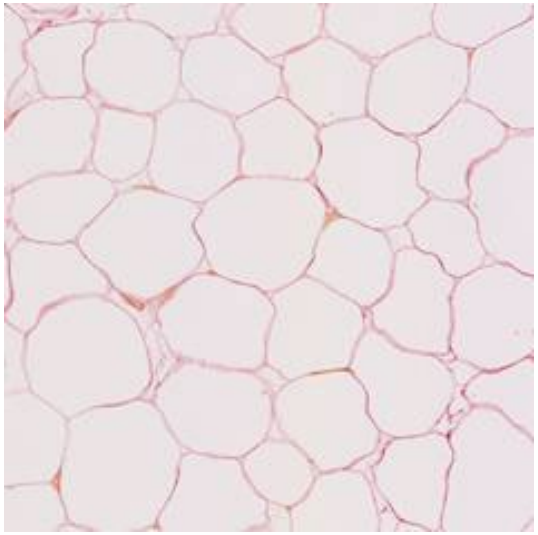
- Age – 43
- Male (%) – 56
- Weight (kg) – 121±21
- BMI (kg/m2) – 41.4±8
- Waist circumference (cm) – 123.8±17.6
- Diabetes - 13%
- NAFLD (33%)
- NAFLD with scar ( 0%)
- HDL 1.18± 0.41mmol/L

Geberhiwot et al. Diabetes 2021;70:364–376
Baig et al. Int J Obes. 2023;47(5):382-390.

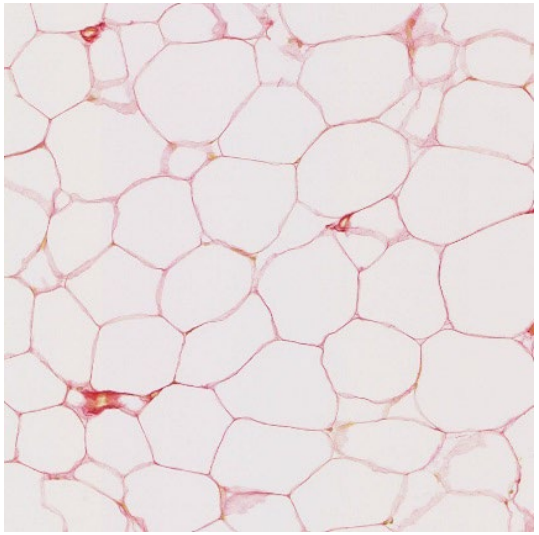
Alstrom

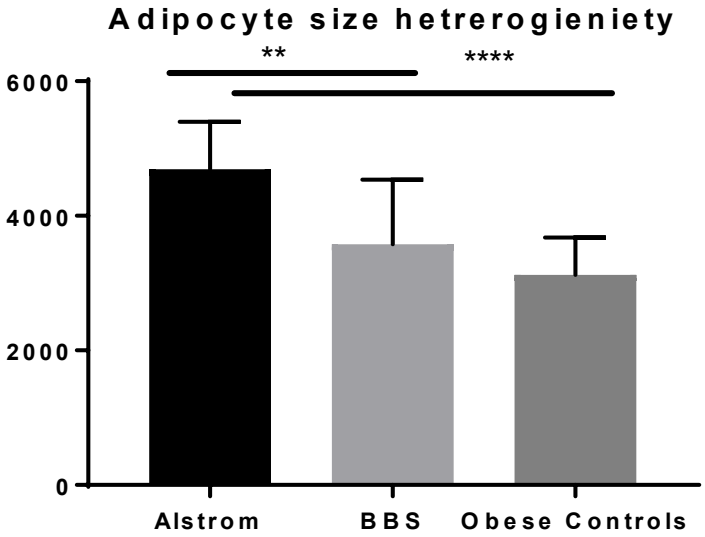


Matched control



BBS



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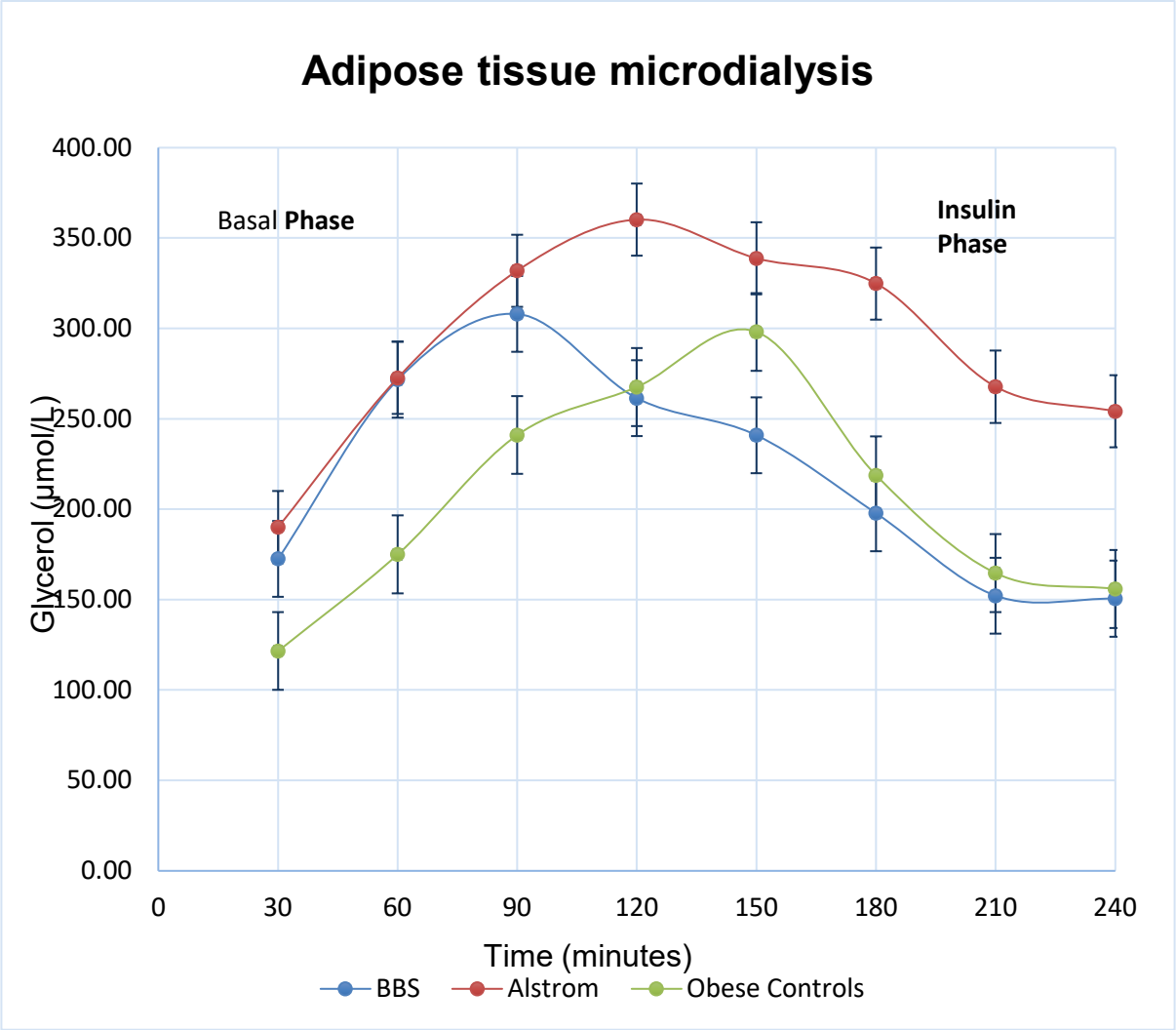
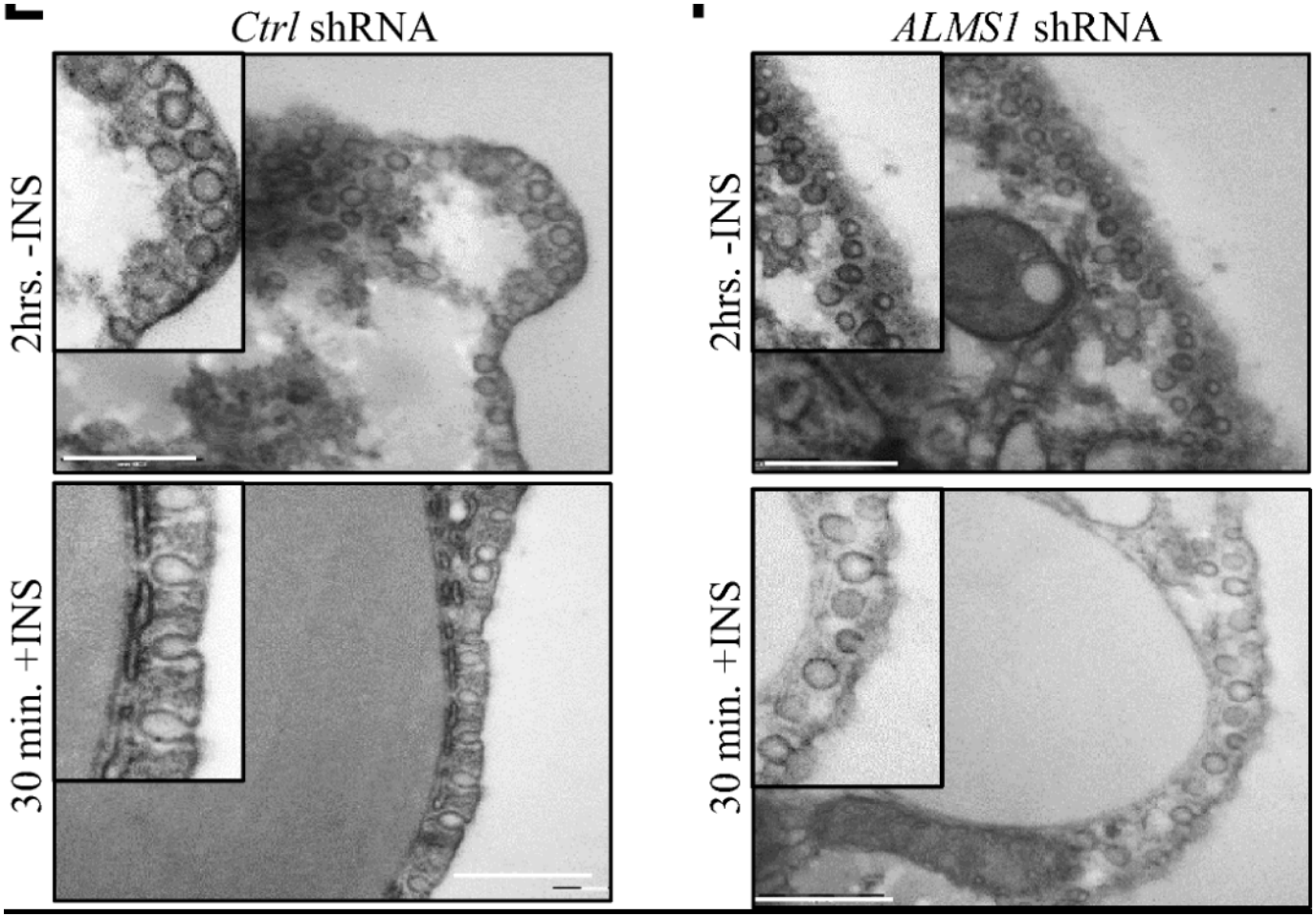



| p-value (BBS vs Alstrom) | |
|---|---|
| AUC 1 (Basal phase) | 0.25 |
| AUC 2 (Insulin phase) | 0.01 |

| Obese controls vs Alstrom | |
|---|---|
| AUC 1 (Basalphase) | 0.01 |
| AUC 2 (Insulin phase) | 0.00 |

Geberhiwot et al. Diabetes 2021;70:364–376
Baig et al. Int J Obes. 2023;47(5):382-390.

AlMS1 is required for GLUT4 sorting vesicles fusion with plasma membrane upon Insulin

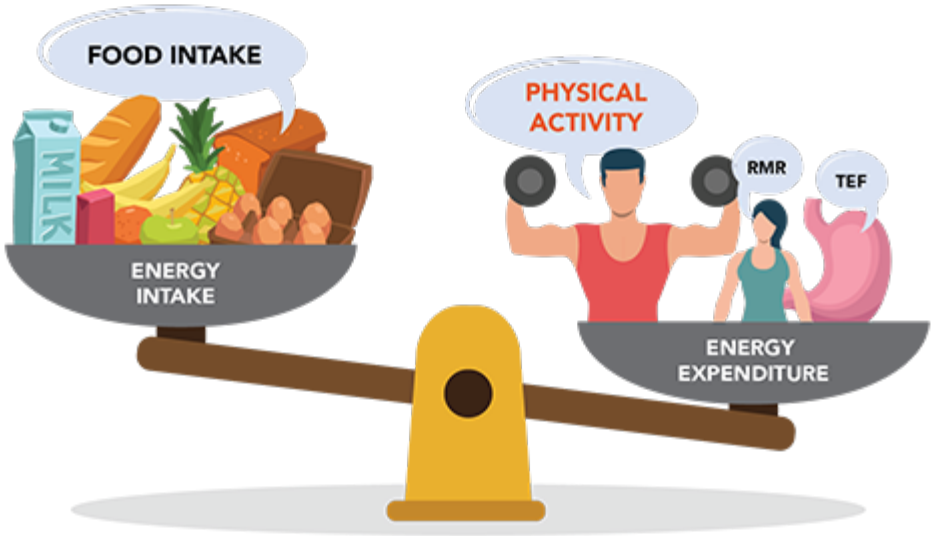



Schreyer E. et al. Diabetes 2022;71:2034–2047

# Summary

- Alstrom subjects IR is disproportionate to their BMI
- IR is driven by adipocyte dysfunction (AD)
- It is the quality not the quantity of fat matter the most
- ALMS mutation → ↓GLUT 4, ↑↑ inflammation/ premature aging.

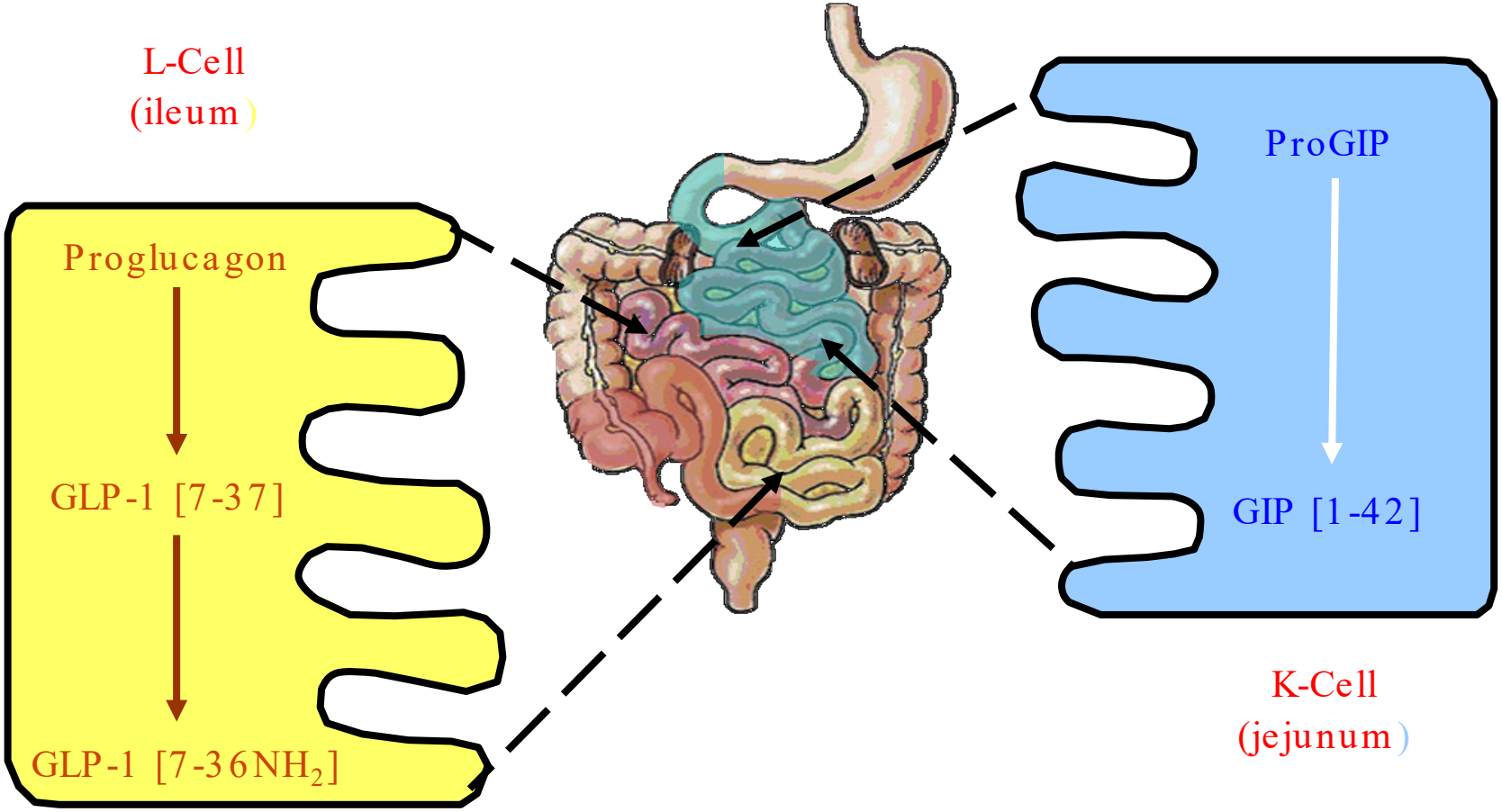
# What can be done to ameliorate metabolic syndrome in Alstrom?



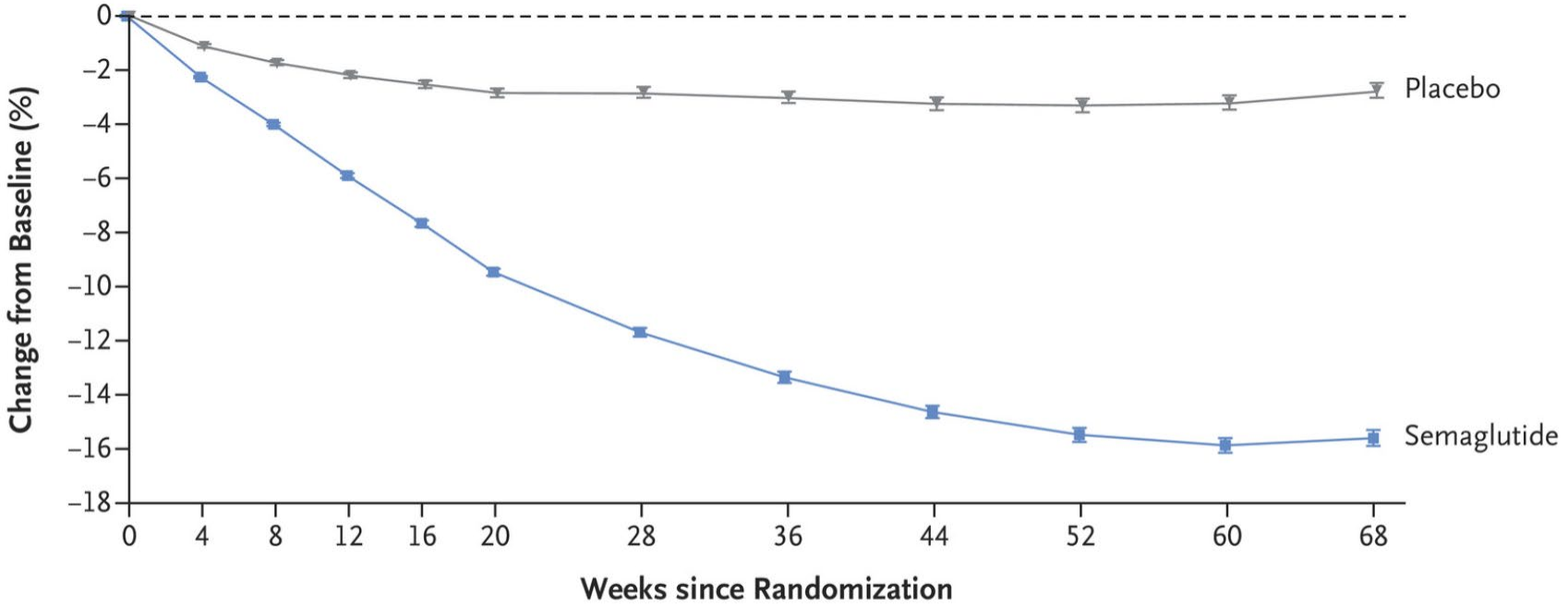
# Glucagon-like-peptide-1 receptor agonist (GLP1RA) in adults with ALMS

long-acting GLP-1 analogs
liraglutide and semaglutide

# GLP-1 and GIP are Synthesized and Secreted from the Gut in Response to Food Intake



# Once-Weekly Semaglutide in Adults with Overweight or Obesity

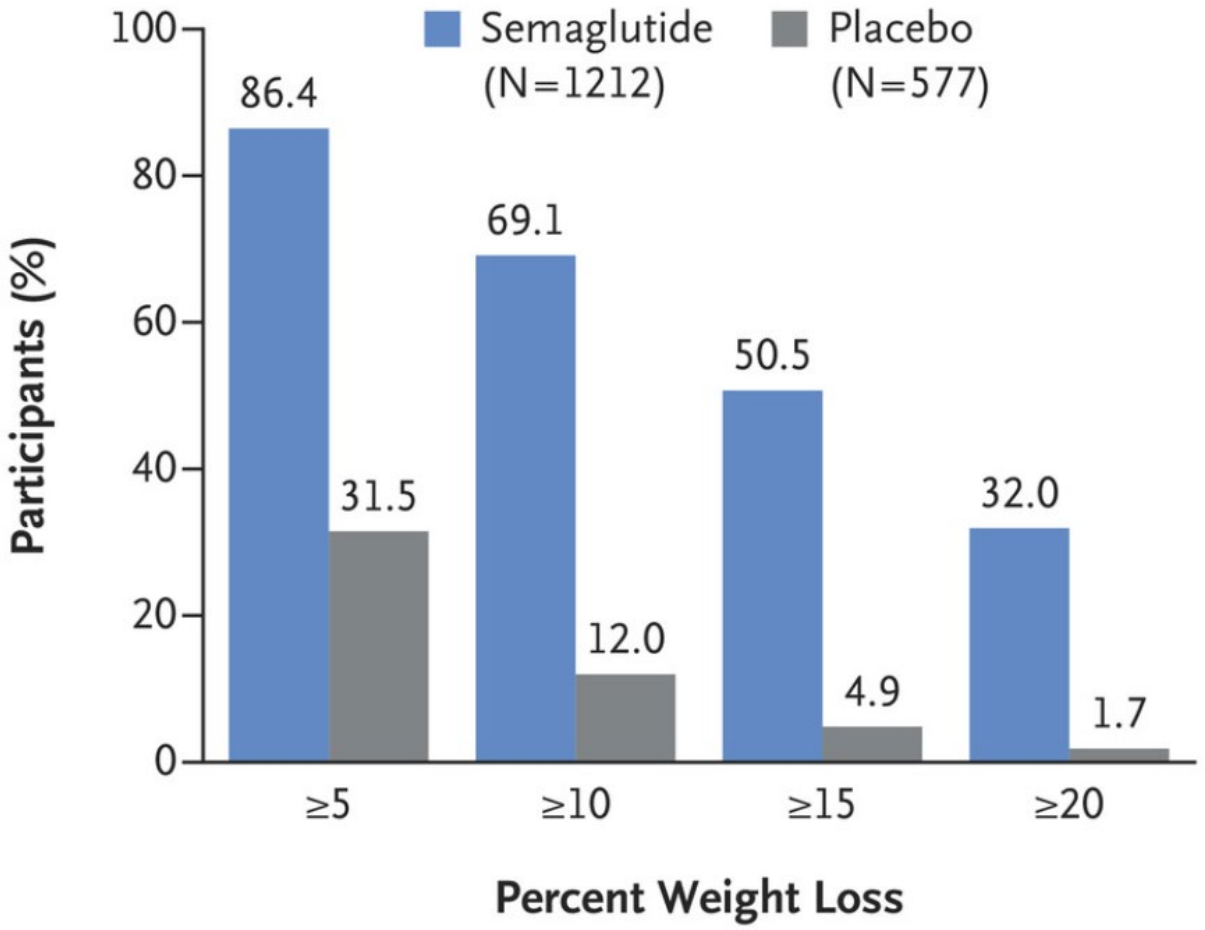



**No. at Risk**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Placebo | 655 | 649 | 641 | 619 | 615 | 603 | 592 | 571 | 554 | 549 | 540 | 577 |
| Semaglutide | 1306 | 1290 | 1281 | 1262 | 1252 | 1248 | 1232 | 1228 | 1207 | 1203 | 1190 | 1212 |

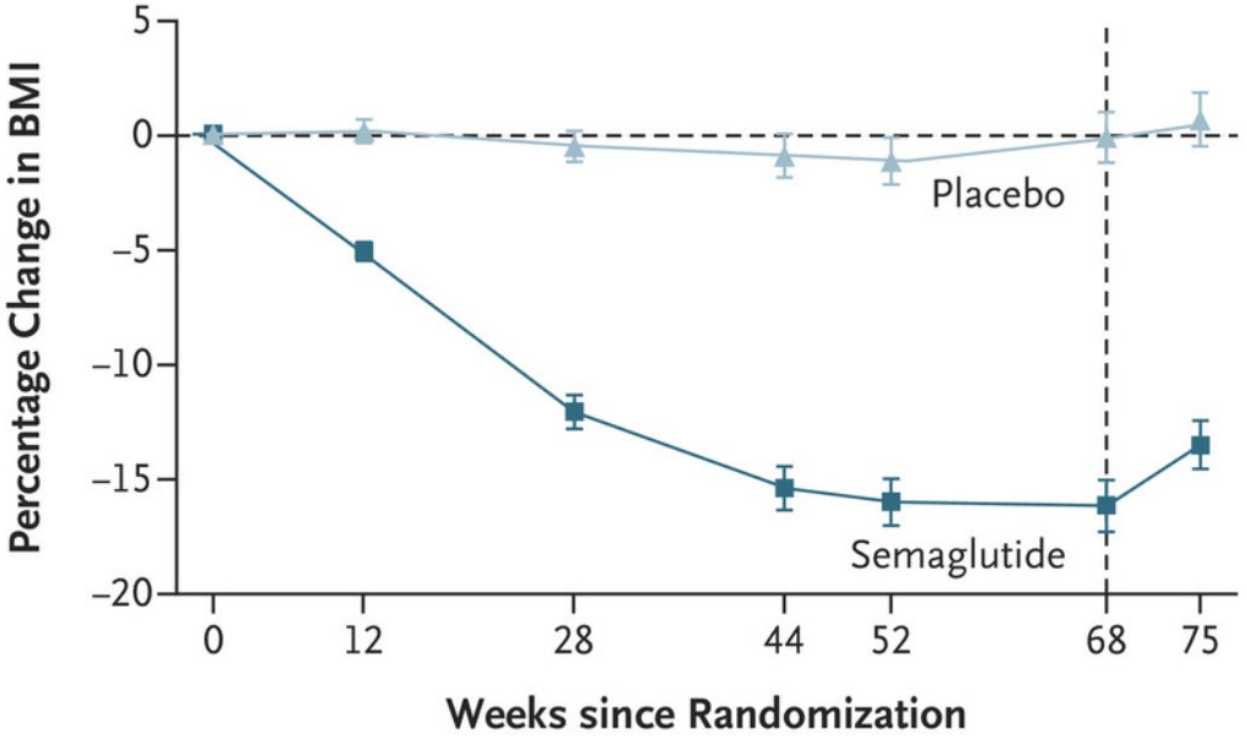
N Engl J Med 2021;384:989-1002.

# Once-Weekly Semaglutide in Adults with Overweight or Obesity (2)



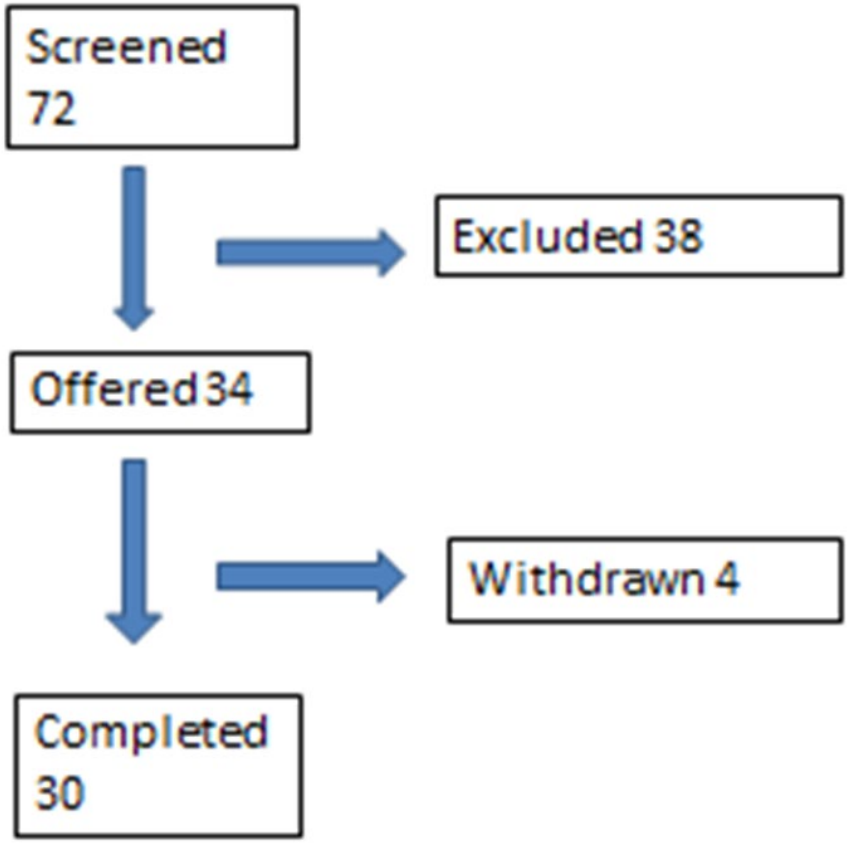

N Engl J Med 2021;384:989-1002.

# Once-Weekly Semaglutide in Adolescents with Obesity




| No. of Participants | | | | | | | |
|---|---|---|---|---|---|---|---|
| Placebo | 67 | 56 | 63 | 61 | 62 | 62 | 61 |
| Semaglutide | 134 | 119 | 131 | 130 | 131 | 131 | 128 |

N Engl J Med 2022; 387:2245-2257

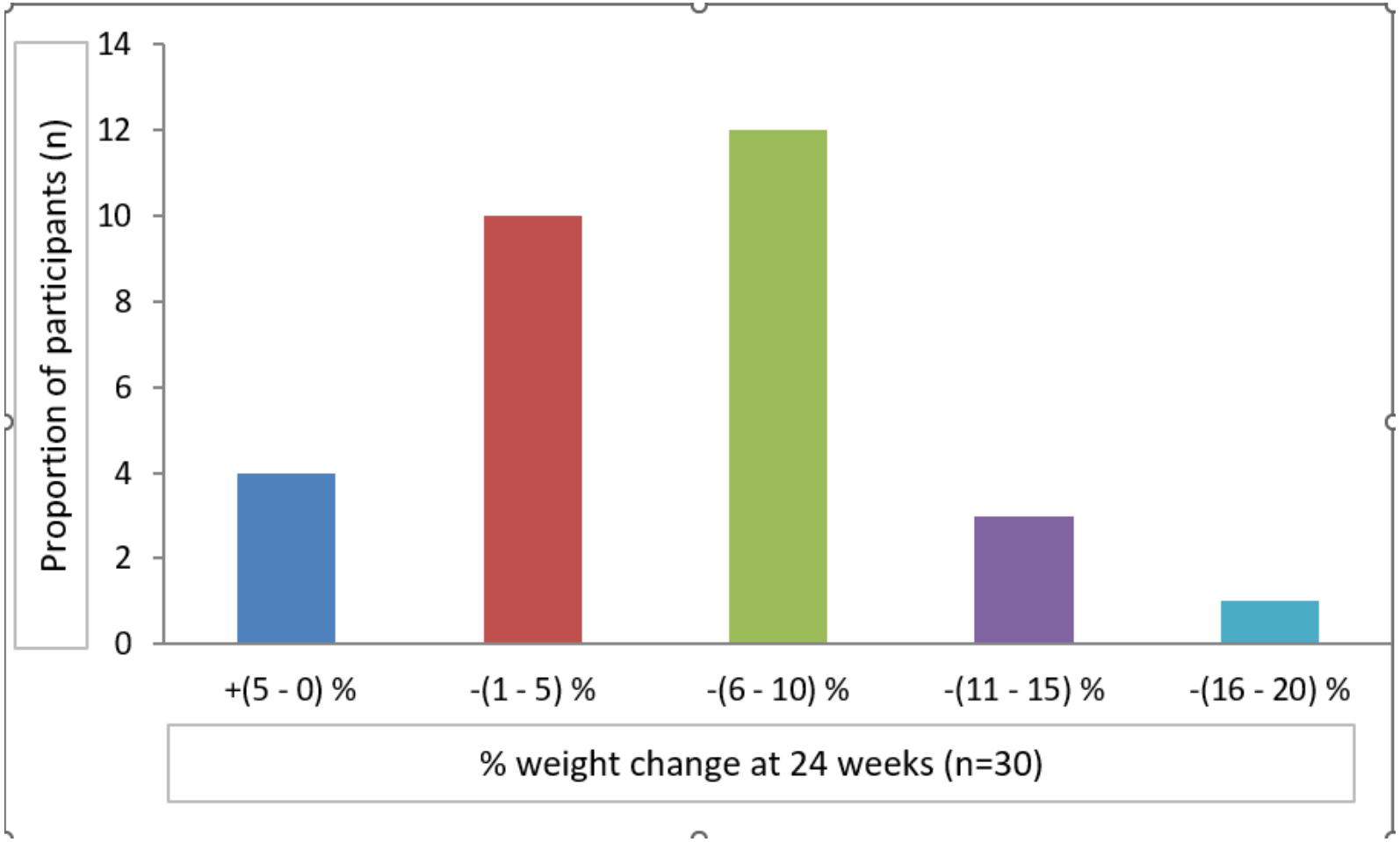

Screened
72
Excluded 38
Offered 34
Withdrawn 4
Completed
30

# Baseline Characteristics of Alström patients treated with GLP-1 analogues

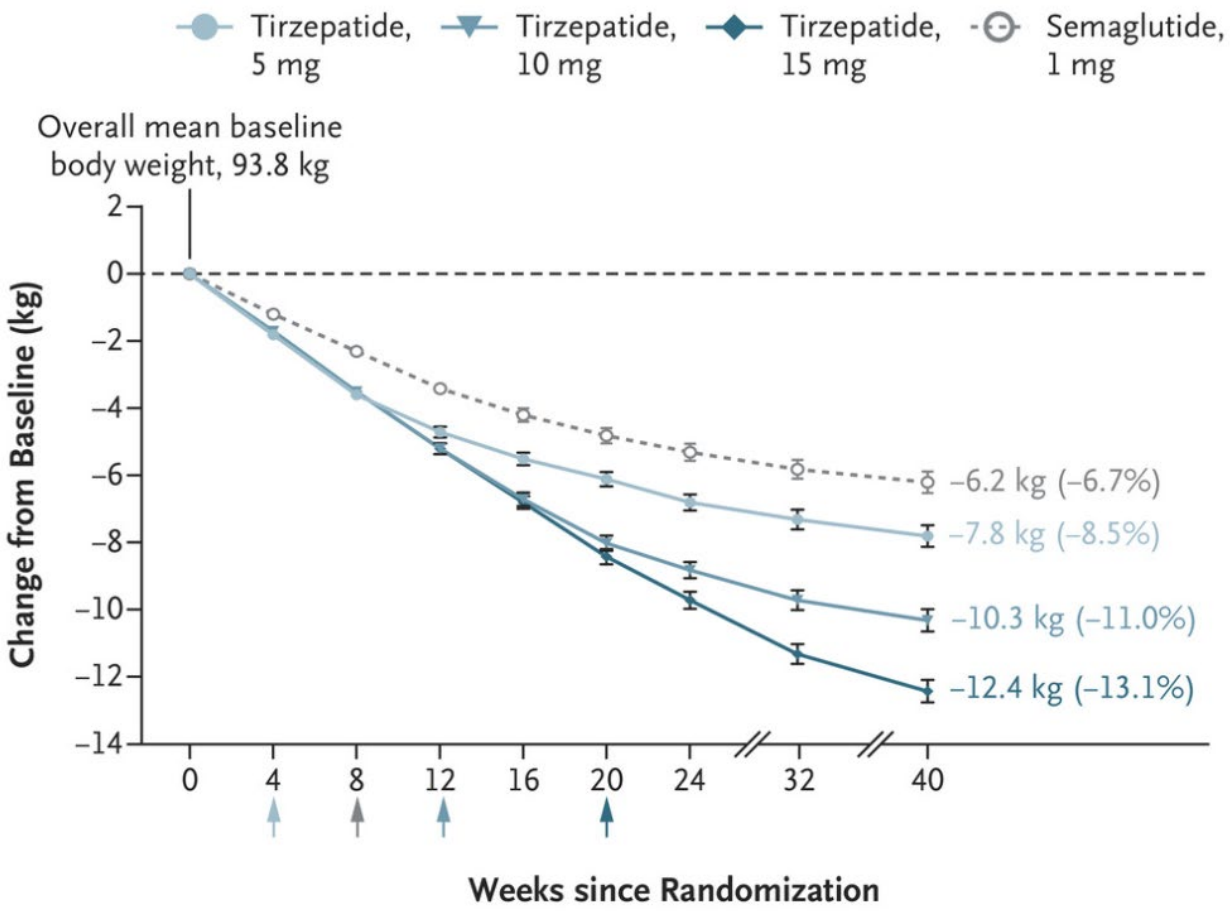
| Characteristics (n=30) | Mean ±SD |
|---|---|
| Age (years) | 31±11 (28) |
| Male, n (%) | 19 (63) |
| Ethnicity, n (%) | British White 20 (67) |
| | British Asian 10 (33) |
| GLP1, n (%) | Exenatide 9 (30) |
| | Semaglutide 21 (70) |
| Insulin(pmol/l) | 4006±1095 |
| HOMA-IR | 344±1029 |
| QUICKI | 0.229±0.03 |
| | |
| Diabetes, n (%) | 23 (77) |
| HTN, n (%) | 21 (70) |
| NAFLD, n (%) | 30 (100) |
| Other AHA, n (%) | Metformin 12 (40%) |
| | SGLT2 8 (27%) |
| | Insulin 8 (27%) |
| | SU 2(7%) |
| | Pioglitazones 3 (10%) |

# Changes in Weight, HbA1c and metabolic parameters over 6 months of treatment with GLP1RA

| Parameters measured | Baseline (Mean ± SD) | 6 months (Mean ± SD) | Mean absolute change | Mean % change | P-value |
|---|---|---|---|---|---|
| Weight(kg)** | 87.7 ± 15 | 82.3 ± 14.4 | 5.4 | 6 | <0.01 |
| BMI (kg/m2) * | 33.5 ± 5.2 | 31.6 ± 5.2 | 2 | 6 | <0.01 |
| Systolic BP (mmHg) | 125 ± 17 | 118 ± 14 | 8 | 6 | 0.03 |
| Diastolic BP (mmHg) | 75 ± 8.7 | 76 ± 8.6 | 0.1 | 0 | 0.96 |
| Glucose(mmol/L) * | 9.8 ± 5 | 8 ± 4.6 | 1.8 | 19 | 0.08 |
| HbA1c(mmol/mol) ** | 68.5 ± 19.6 | 56.5 ± 17.9 | 12 | 18 | <0.01 |
| C-Peptide(pmol/l) *** | 3203 ± 2068 | 3618 ± 1827 | 415 | 13 | 0.28 |
| TG (mmol/L) * | 3.3 ± 1.9 | 2.5 ± 1.1 | 0.8 | 24 | 0.01 |
| TC (mmol/L) * | 4.5 ± 1.3 | 3.8 ± 0.9 | 0.7 | 15 | 0.03 |
| LDL-C(mmol/L) *[1] | 2.3 ± 0.6 | 1.9 ± 0.7 | 0.4 | 18 | 0.03 |
| HDL (mmol/L) * | 0.9 ± 0.2 | 1 ± 0.3 | -0.1 | 8 | 0.02 |
| ALT(IU/L) * (Median, IQR) | 65, 104-33 | 53,87-30 | 12 | 18 | 0.04 |
| AST(IU/L) **** | 42 ± 25 | 33 ± 19 | 9 | 21 | 0.08 |
| ELF score *[2] | 9.8 ± 0.6 | 9.7 ± 0.7 | 0.1 | 1 | 0.34 |
| Urea(mmol/L)* | 7.5 ± 3.9 | 7 ± 3.5 | 0.4 | 6 | 0.22 |
| Creatinine(umol/L) * (median, IQR) | 89,125-69 | 93,141-74 | -4.0 | 4 | 0.12 |
| e GFR(ml/min) * | 74.2 ± 21.3 | 73.9 ± 23.1 | 0.3 | 0.4 | 0.81 |

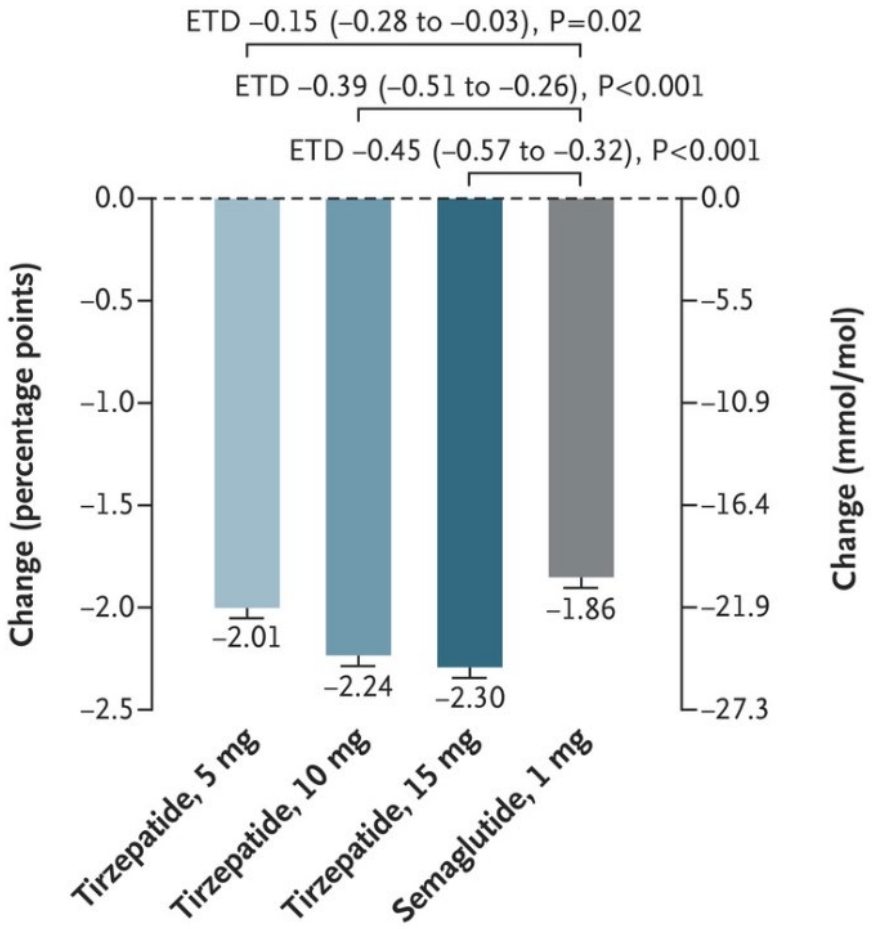

Proportion of participants (n)
14
12
10
8
6
4
2
0
+(5 - 0) %
-(1 - 5) %
-(6 - 10) %
-(11 - 15) %
-(16 - 20) %
% weight change at 24 weeks (n=30)

# Effect of Once-Weekly Tirzepatide, as Compared with Semaglutide, on Body Weight




N Engl J Med 2021; 385:503-515

# Changes in overall  blood sugar control




N Engl J Med 2021; 385:503-515

# Summary

- Patients with Alstrom syndrome have a poor-quality fat cells
- Weight loss is difficult but small weight loss can make big difference
- Good metabolic control increase survival by at least 20 years for most patients with ALMS.
- Long acting GLP1RA are safe and effective in patients with Alstrom syndrome

# Acknowledgments


- Patients and families
- ASUK
- Clinical and Research team
- International collaborates