

Bariatric Surgery-  
Induced Epigenetic  
Changes: miRNA  
and  
Metabolomic  
Profiling in Obese,  
Obese Diabetic, and  
Obese  
Pre-Diabetic  
Patients



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# Conflict of Interest

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- I have no financial disclosures





# Ethical Considerations

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- Ethical approval have been obtained from the Institutional Review Board (NMRR and MREC)
- Written informed consent have been collected from all participants.

# Bariatric Surgery Challenges

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- Clinical benefits, such as remission of metabolic syndrome, are well-recognized
- Varied clinical outcomes amongst patients
- The underlying molecular mechanisms driving these positive outcomes are not fully understood
- Limited understanding about the molecular and epigenomic effects of bariatric surgery



# Bariatric Surgery Challenges

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- Hinders our ability to predict which patients will respond most favorably to surgery and leaves us without molecular targets for improving post-surgery care
- Studying changes in miRNA profiles before and after bariatric surgery
- Identifying specific miRNAs that are over- or under-expressed post-surgery could offer valuable insights into the mechanisms underlying varied patient outcomes
  - suggest potential targets for therapeutic intervention or preventive measures





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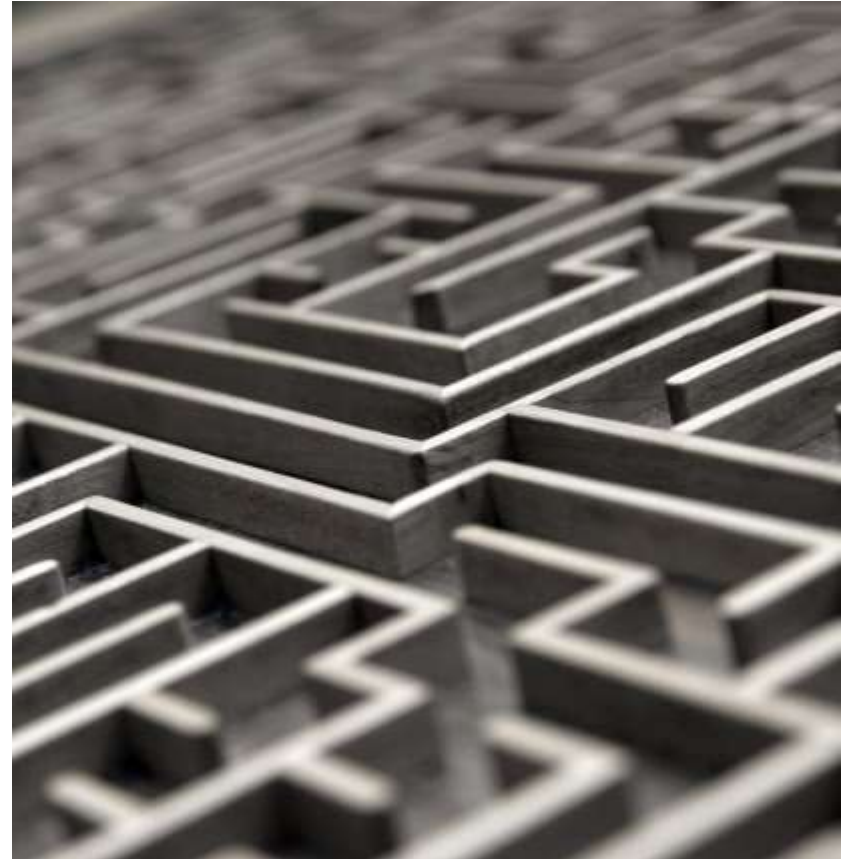
## Research Question

"How do miRNA profiles change post-bariatric surgery, especially those miRNAs linked with significant health implications such as diabetes and cancer?"

# Primary Objective

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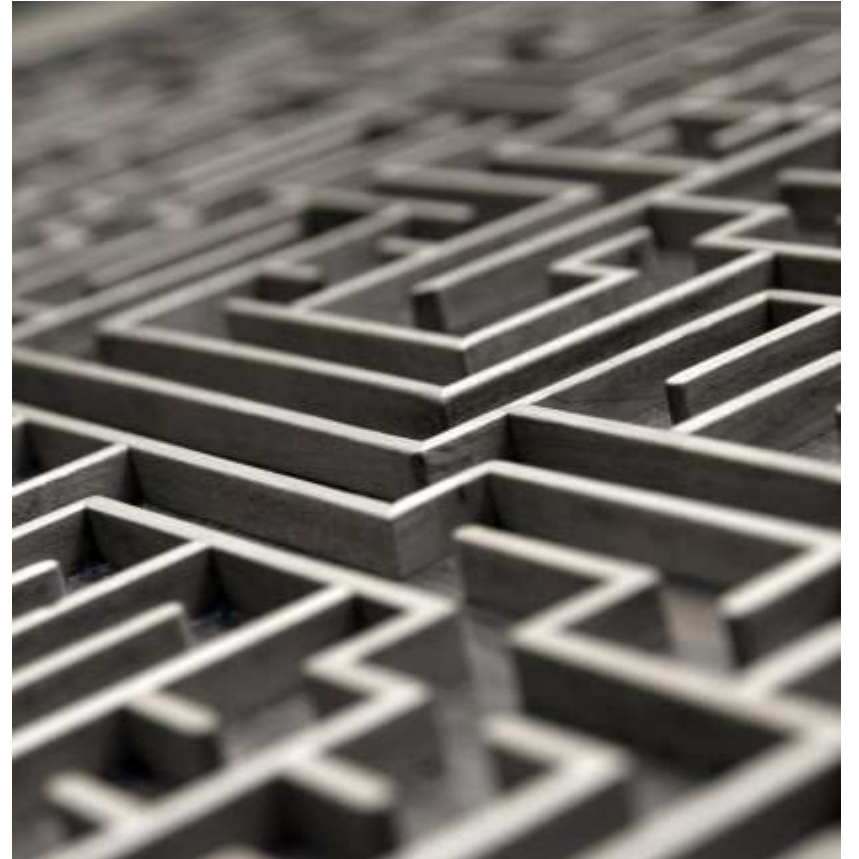
- To longitudinally analyze and characterize the changes in miRNA profiles in patients undergoing bariatric surgery, focusing on miRNAs that have known associations with significant health implications like cancer and metabolic disorders



# Secondary Objectives

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1. To correlate these epigenetic shifts in miRNA profiles with clinical markers and outcomes, such as metabolic syndrome remission, weight loss, and changes in blood glucose levels.
2. To identify potential predictive miRNA markers that could help tailor post-surgical interventions and monitoring.
3. To explore the long-term health implications, particularly in cancer risk and metabolic health, based on the changes observed in the miRNA profiles

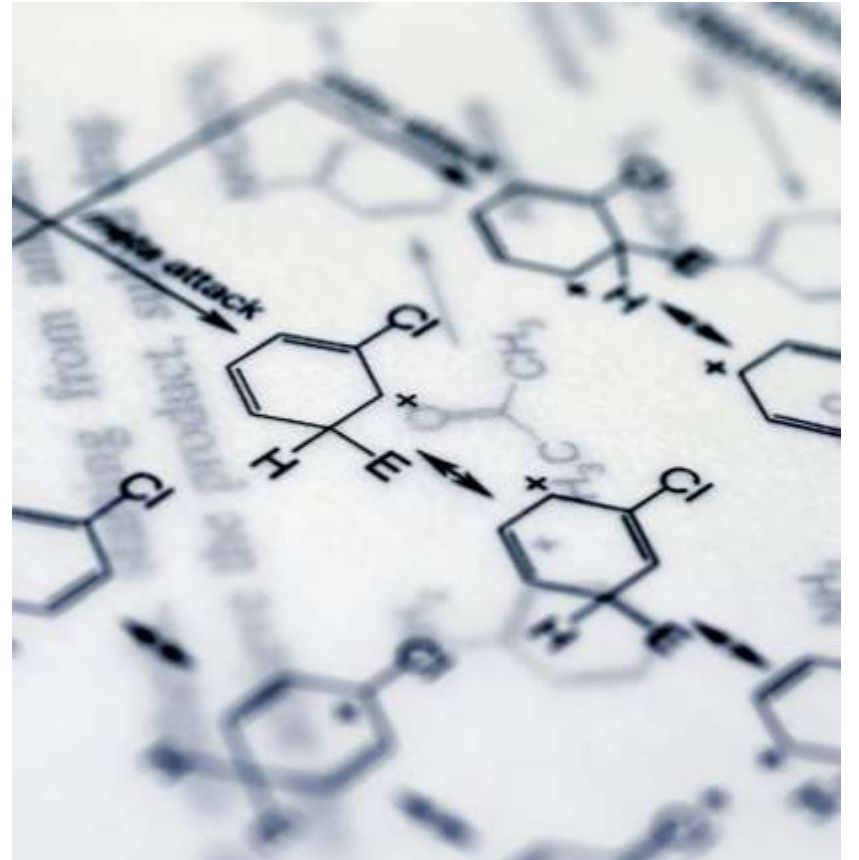




# Methodology

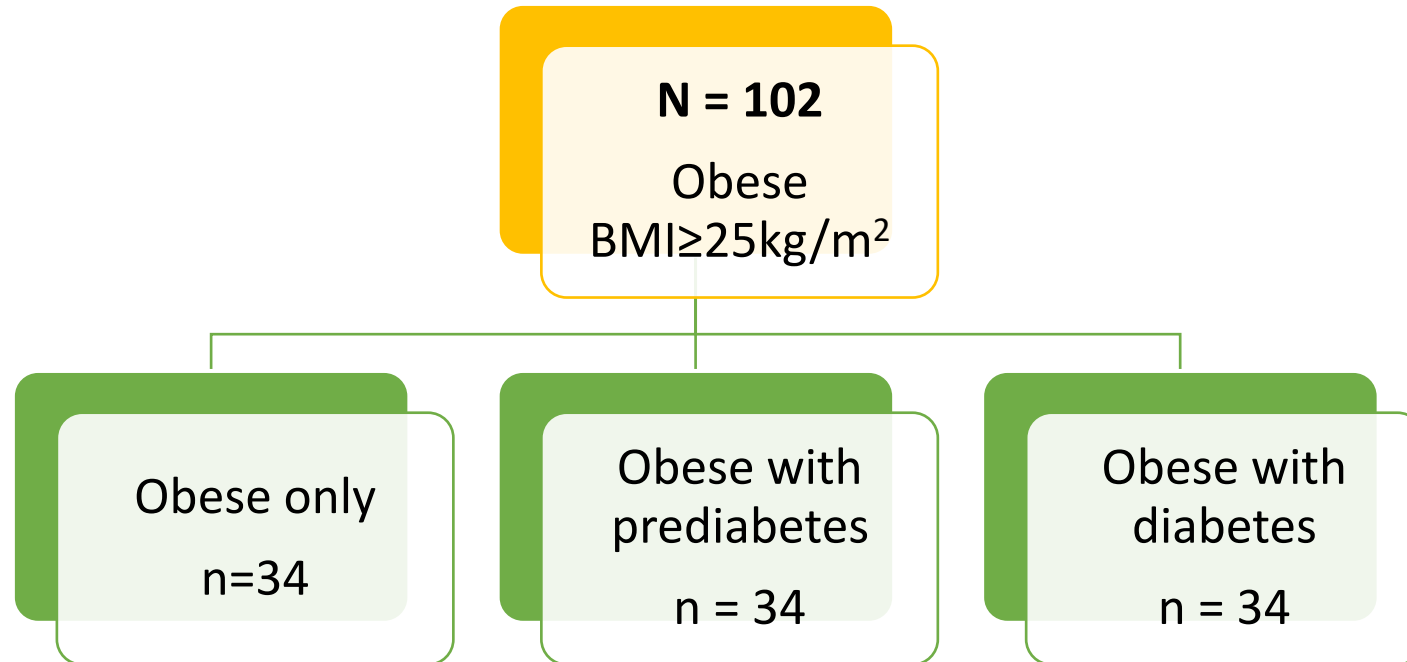
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- **Study Design**
- Longitudinal Cohort Study
- **Sample Size:**
- 102 subjects undergoing bariatric surgery
- Multi-centre study
- BMI  $\geq 25\text{kg/m}^2$  (Asian BMI: WHO/IASO/IOTF, 2000)



# Methodology – Study Groups

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# Methodology

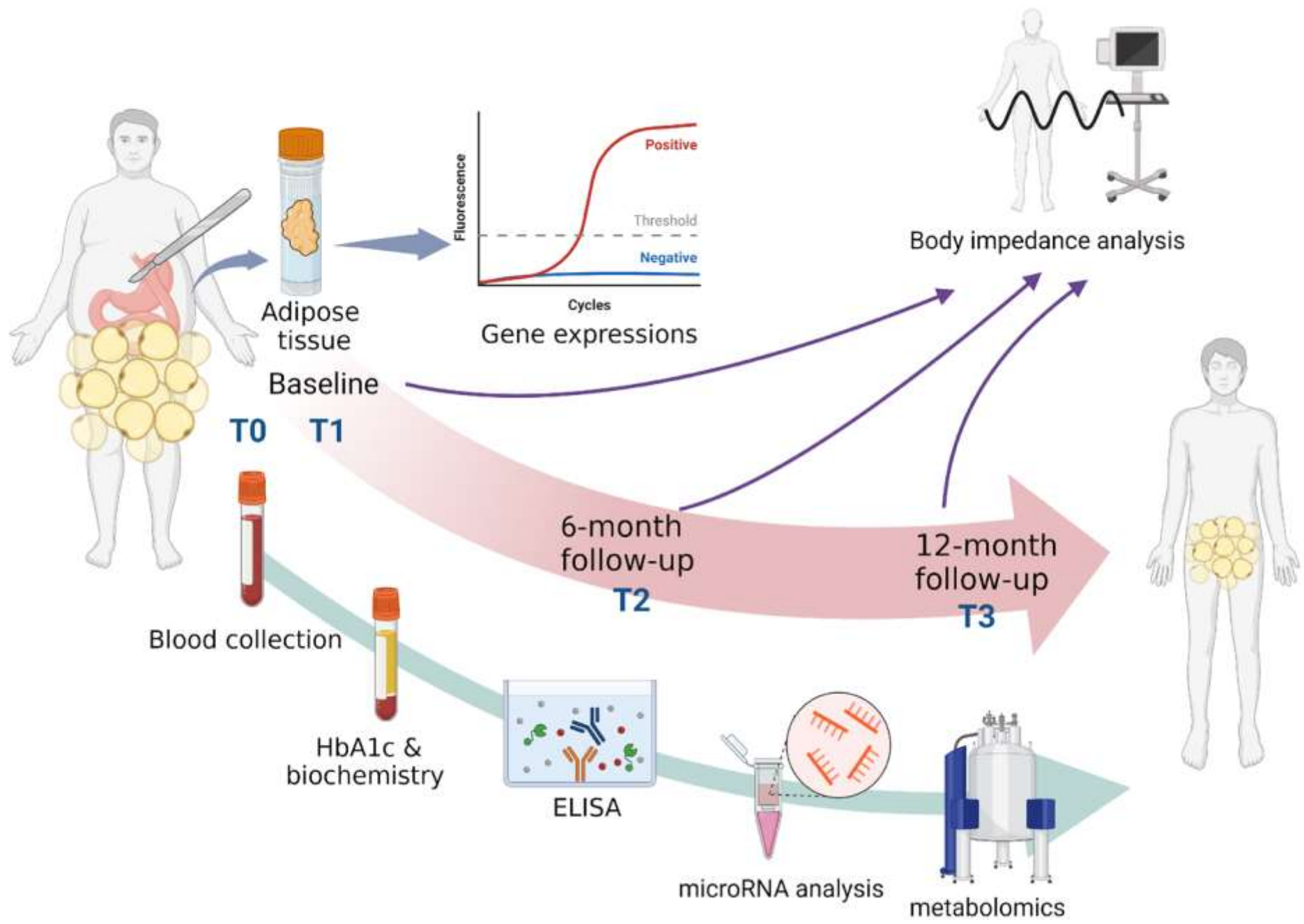
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## Inclusion Criteria

1. BMI  $\geq 25$  kg/m<sup>2</sup>
2. Men and women Ages 18-65 years old
3. Pre-diabetes /diabetes (based on groups)

## Exclusion Criteria

1. BMI  $< 25$  kg/m<sup>2</sup>
2. Use of medications that may affect body weight at screening or during a 3 month period prior
3. Other medical conditions like Cushing's, acromegaly, Heart failure, Crohn's disease, etc.
4. Alcohol dependence





# microRNA levels

- miRNAs are small noncoding RNAs that act as regulators of gene expression
- Dysregulation of miRNAs has been shown to contribute to multiple disease processes.
- We tested 84 miRNAs (mainly in diabetes-related, but not limited to)

# miRNA Profiling

- **RNA Isolation:**
- Using a standardized protocol to extract total RNA from blood samples
- **miRNA Sequencing:**
- Next-generation sequencing to identify miRNA profiles
- **Target miRNAs:**
- Special focus on hsa miR 107, hsa miR 19a-3p, hsa miR 451a, hsa miR 365a-3p, hsa miR 361-5p, hsa miR 125b-5p, and hsa miR 375-3p.

# Results

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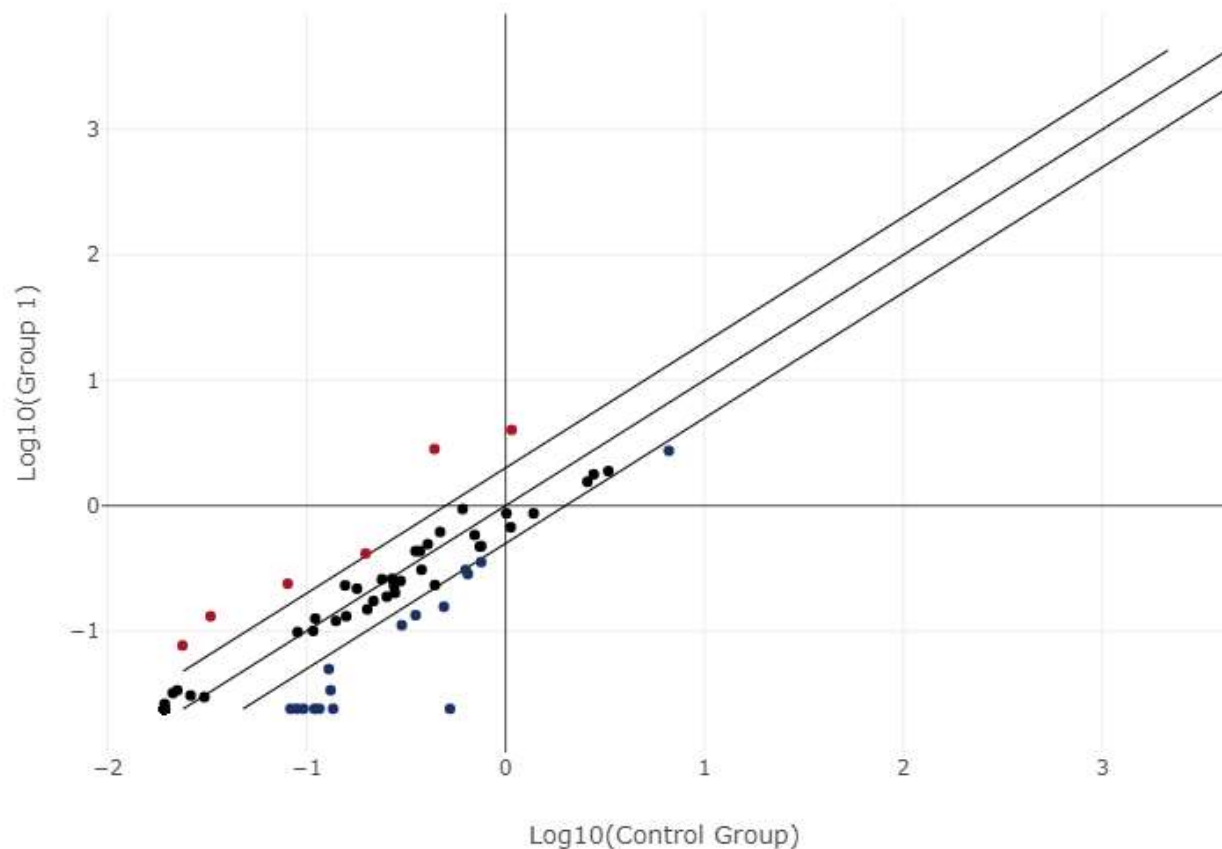
- Interim Analysis at 6 months
- Metabolomic results are not available yet



	Baseline	6 month follow-up	P-value	
BMI	38.99 ± 1.867	29.48 ± 1.496	0.0002***	↓
HbA1c (%)	5.818 ± 0.1819	4.989 ± 0.06594	< 0.0001***	↓
Total cholesterol (mmol/L)	5.096 ± 0.1467	5.047 ± 0.1305	0.8042 Not significant	↔
Body fat mass (kg)	50.27 ± 3.896	31.40 ± 2.932	0.0003***	↓
Skeletal muscle mass (kg)	32.10 ± 1.735	25.51 ± 1.201	0.0024**	↓
Visceral fat area (kg)	207.6 ± 10.37	146.1 ± 12.52	0.0005***	↓
Phase angle (unit)	6.487 ± 0.1744	5.018 ± 0.1315	< 0.0001***	↓



# Scatter plot of patients miRNA baseline vs. 6 month follow-up



Red dot: upregulated > 2-folds

Blue dot: downregulated > 2-folds

Black dot: downregulated < 2-folds

# Over-expressed miRNA

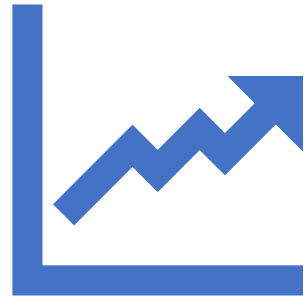
miRNA	Fold-change	Function
hsa-let-7i-5p	3.23	related to glucose metabolism and insulin sensitivity
hsa-miR-107	6.44	is one of the most promising miRNAs in evaluating diabetes and insulin sensitivity
hsa-miR-130a-3p	2.10	Play a critical role in diabetes-related complications; associated with insulin exocytosis.
hsa-miR-19a-3p	2.97	endothelial miR-19a is involved in vascular homeostasis and atheroprotection
hsa-miR-29a-3p	3.99	related to T2DM, gestational diabetes and deterioration of glucose tolerance
hsa-miR-451a	3.75	Downregulation of miR-451a in plasma may promote prothrombin expression and contribute to high blood coagulation state in gestational diabetes mellitus.

# Under-expressed miRNA

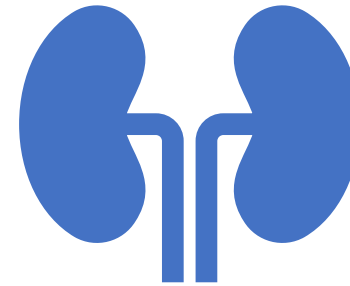
miRNA	Fold-change	Function
hsa-miR-125a-5p	-2.70	attenuates diabetic retinal impairment
hsa-miR-125b-5p	-3.13	Associated with pancreatic $\beta$ -cell function
hsa-miR-135b-5p	-2.64	might have a role in atherosclerosis pathogenesis; known to be associated with cancer, mediating inflammatory responses
hsa-miR-148a-3p	-2.27	alleviates high glucose-induced diabetic retinopathy; can be potential biomarkers for diagnosis of pre-diabetes and type 2 diabetes; associated with HbA1c levels.
hsa-miR-15b-5p	-2.60	High glucose elevated miR-15b-5p expression
hsa-miR-3121-3p	-2.05	schizophrenia and obsessive-compulsive disorder
hsa-miR-361-5p	-3.91	associated with prognosis in patients with breast cancer.
hsa-miR-365a-3p	-21.88	Regulated in colon cancer tissues, is involved in tumor progression, and regulates cancer cell behavior
hsa-miR-375-3p	-4.02	was involved in cardiac dysfunction and cardiogenesis

Not directly related but interesting to know, might due to changes in the brain

# Translating Findings to Practice – Diagnostic Applications



Potential predictive tool for reduced cancer risk.



Monitoring tool for glucose metabolism post-surgery.

# Translating Findings to Practice – Therapeutic Implications



Personalized post-operative care  
based on miRNA profile.



Tailored interventions to support  
pancreatic health.

# Discussion

## Key Points:

- Downregulated hsa miR 365a-3p may serve as a potential predictive marker for reduced colon cancer risk.
- Downregulated hsa miR 361-5p may indicate better prognosis in breast cancer patients.

## Clinical Implication:

- Downregulation of these miRNA may suggest a reduced risk for colon and breast cancer post-bariatric surgery

# Discussion

## Key Points:

- Under-expression of hsa miR 125b-5p correlated with changes in insulin production or secretion.
- Potential link with improved or worsened glucose metabolism.

## Clinical Implication:

- Regular monitoring of hsa miR 125b-5p levels could serve as a diagnostic measure for tailoring glucose management strategies post-surgery

# Discussion

## Key Points:

- Reduced hsa miR 125b-5p expression might warrant targeted interventions to support pancreatic beta-cell function.
- Possible therapeutic avenues: Use of miRNA mimics, lifestyle adjustments, or pharmacological interventions aimed at pancreatic health.

## Clinical Implication:

- Interventions tailored to restore or modulate hsa miR 125b-5p levels could offer therapeutic options for improving glucose metabolism post-surgery.



# Strengths

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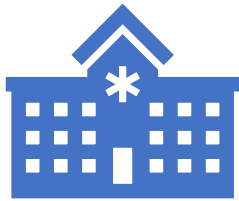
- 1. Longitudinal Design:** Capturing data at multiple time points allows for better tracking of epigenetic changes over time.
- 2. Targeted miRNA Analysis:** The study focuses on miRNAs with known associations to significant health conditions like cancer and metabolic disorders, making the findings immediately relevant.
- 3. Clinical Correlations:** The study aims to correlate miRNA expression changes with clinical markers, providing a direct link between molecular changes and patient outcomes.
- 4. Interim Insights:** The 6-month data provide early insights that may guide immediate clinical decision-making and inform subsequent phases of the study.
- 5. Ethical Rigor:** Informed consent and strict ethical guidelines ensure the credibility of the study.

# Limitations

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- 1. Limited Time Frame:** The 6-month interim analysis may not capture the full spectrum of long-term epigenetic changes post-surgery.
- 2. Sample Size:** With 102 subjects, the sample size may limit the generalizability of the findings.
- 3. Lack of Control Group:** Without a non-surgical control group, it's challenging to isolate the effects of surgery from other factors like lifestyle changes.
- 4. Interim Nature:** As an interim analysis, the results are preliminary and subject to change as more data are collected.
- 5. Technological Constraints:** The methodology relies on current miRNA sequencing technologies, which have their own limitations in sensitivity and specificity.

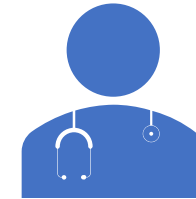
# Conclusion and Future Directions



The transformative potential of personalized care post-bariatric surgery.



The need for further research on the wider spectrum of miRNAs and health outcomes.



Emphasis on the promise of merging surgical interventions with molecular insights.