Polycystic Ovarian Syndrome in Adolescents: Discovery Proteomics and the Search for Novel Non-Invasive Biomarkers

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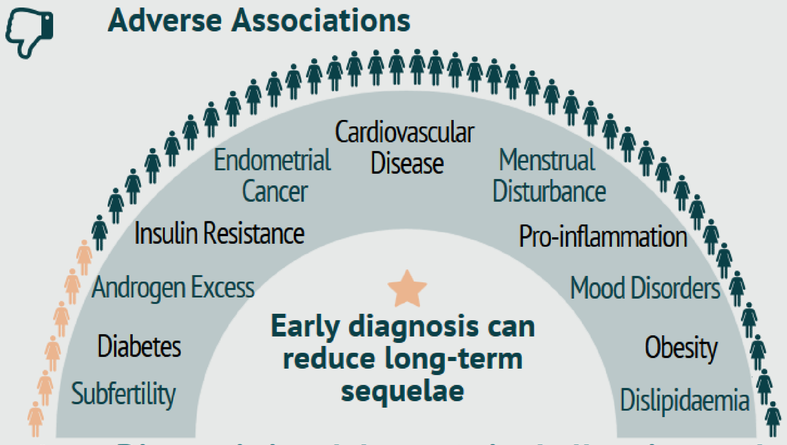
Introduction

PCOS affects 4-20% of females

Polycystic ovarian syndrome (PCOS) is the most common hormone disorder in females

Adverse Associations



Diagnosis in adolescents is challenging as the following are common:

- Clinical signs of hyperandrogenism (e.g. acne)
- Anovulatory cycles and irregular periods
- Poly/multicystic ovarian morphology

Proteomics

Enables better understanding of disease mechanisms and facilitates identification of novel biomarkers

Aims

1. To describe the clinical phenotype of PCOS in adolescents
2. To undertake deep phenotyping discovery proteomic urine profiling using label-free quantitative proteomics (nano 2D-LC-QToF-MS^e)

Methods

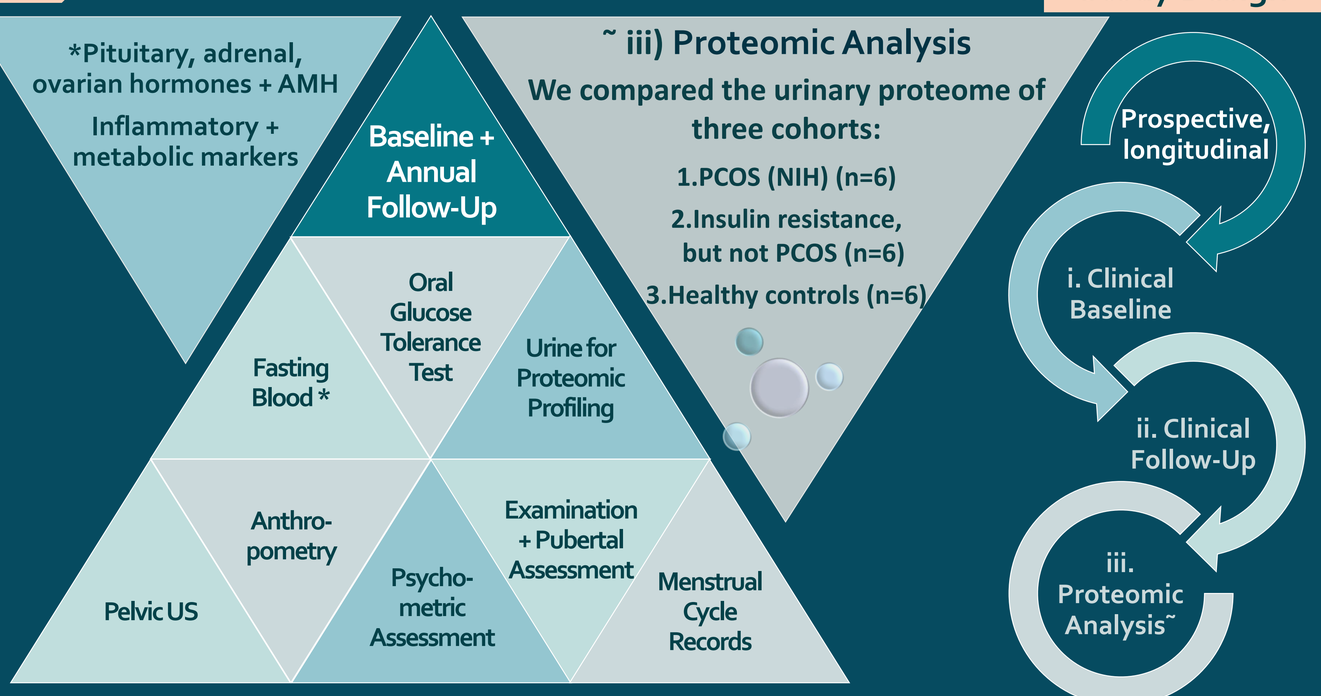
Participant Selection Criteria

Females aged 12-19 years

Adolescent Endocrine/ gynae Clinics

Referred as suspected PCOS

Study Design



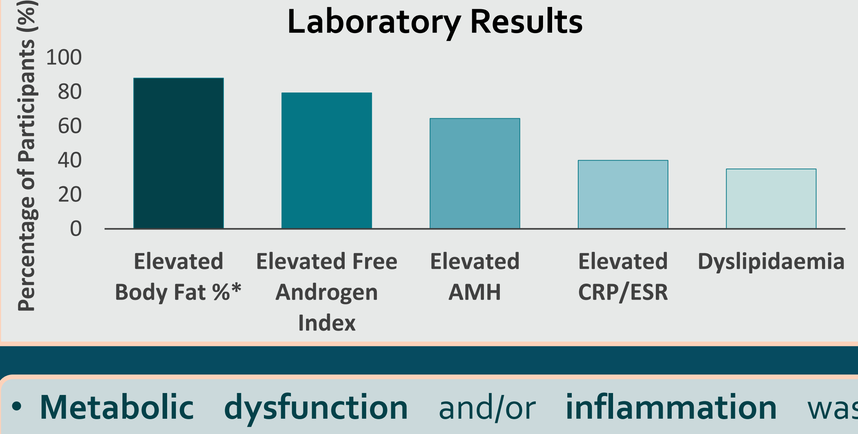
Results

Baseline Demographics

- 40 participants have been recruited
- Median age 15.0 y (range 12.5-18.3 y)
- Mean age at menarche 10.9 y (SD 1.38)
- Tanner stage: IV (n=18) and V (n=22)

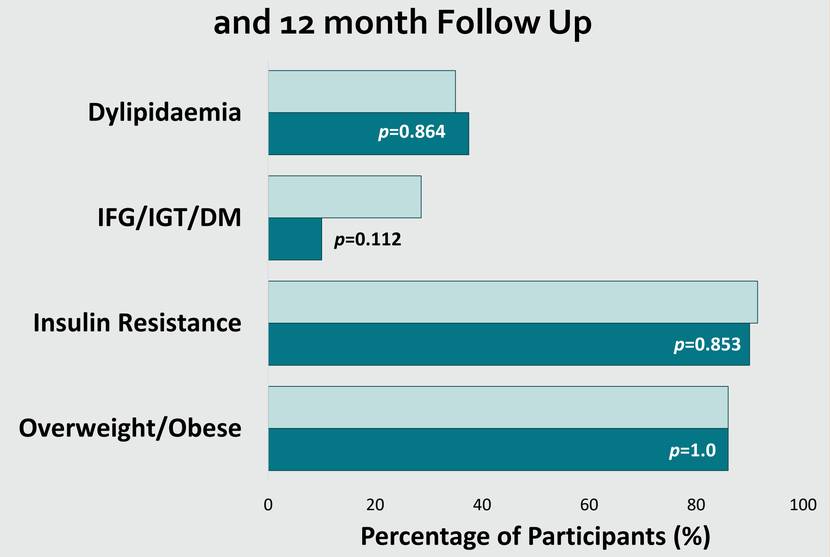
Figure 1: Clinical Signs at Presentation (n=40)

Figure 2: Baseline Anthropometric and Laboratory Results



- **Metabolic dysfunction** and/or **inflammation** was almost universal and did not change from baseline to follow-up despite intervention: lifestyle (27%), COCP ± anti-androgen (16%), metformin (30%), metformin + COCP ± anti-androgen (27%). **(Fig. 1-3)**
- **Anxiety** & **depression** were common but <50% of these were known to mental health services
- Only 3 participants had evidence of PCOS on **pelvic ultrasound.** A further 8 had equivocal results

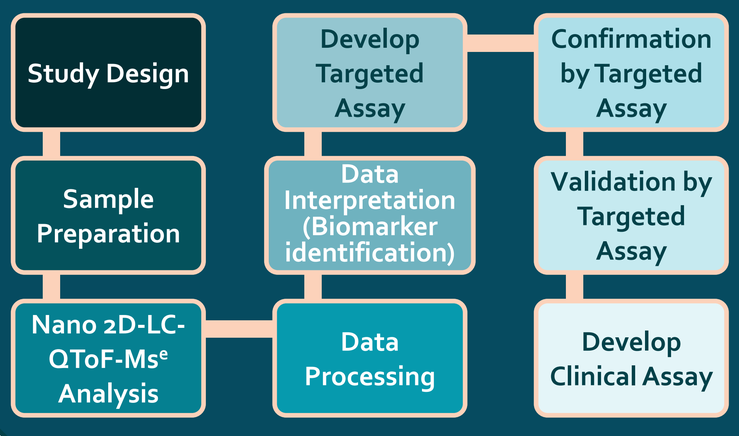
Figure 3: Metabolic Dysfunction at Baseline and 12 month Follow Up



Definitions & Abbreviations

- *Normal range body fat 16.9-29.9%
- **Elevated free androgen index** (>4.5%):
  - Median FAI improved at follow up; baseline 6.7% [IQR 4.6-12.0%], FU 2.6% [IQR 0.5-5.7], (p=0.002)
- **Elevated AMH** (>28pmol/l): Median AMH 34pmol/l [IQR 18-48 pmol/l)
- **Insulin resistance (IR):** Whole body insulin sensitivity <4.5% (Matsuda Index)
- **IFG/IGT:** Impaired fasting glucose/glucose tolerance
- **DM:** Diabetes Mellitus (Type 2)

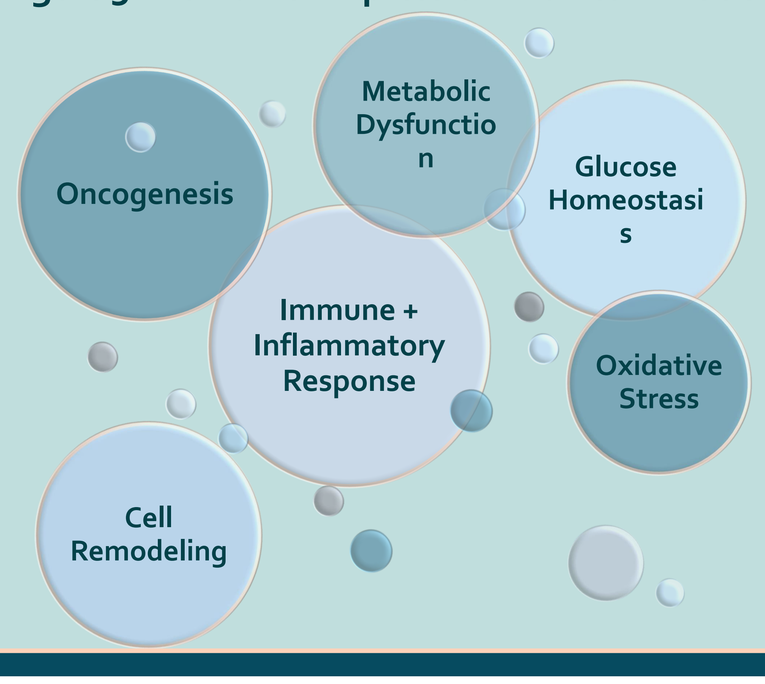
Figure 4: Biomarker Discovery Process



Discovery (Label-free) Proteomics (Fig. 4)

- We identified >**4,000 urinary proteins** across three cohorts (PCOS, IR, controls).
- Following multivariate and univariate analysis, we identified **>100 biomarkers of significance** which were differentially expressed in PCOS samples in comparison to either IR or controls (p<0.05).
- Of these, **1/3 were upregulated in PCOS** and **2/3 were downregulated.**
- Protein (biomarker) expression profiles revealed associations between these significant biomarkers and the following processes: (Fig. 5).

Figure 5: Biomarker Expression Profiles in PCOS



Conclusions & Future Directions

- **Adolescents with PCOS are at high risk of metabolic & pro-inflammatory dysfunction & mental health disorders.**
- Early diagnosis and intervention can reduce long-term sequelae but current management options are often ineffectual.
- Current diagnostic and surveillance methods for PCOS are suboptimal and improved methods are urgently required.
- **We describe the use of urinary proteomics** to study metabolic pathways affected in PCOS and the identification of novel non-invasive biomarker candidates.
- Subsequently, we will validate and quantitate these findings in a larger cohort.
- We will then create a **non-invasive clinically translatable multiplex assay** to aid diagnosis and stratify management of this common adolescent condition (Fig. 4.)

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58ESPE RFC11-003

Sex differentiation, gonads and gynaecology or sex endocrinology

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Poster presented at: ESPE 2019 VIENNA

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