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PREDICTORS OF THE DEVELOPMENT OF CYSTIC FIBROSIS-RELATED DIABETES (CFRD)

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Background

- CFRD is a common complication of CF, associated with increased morbidity and mortality.
- Early identification of CF patients at risk for developing CFRD would allow close supervision and early treatment
- Annual OGTT is the screening test of choice for diagnosis of CFRD from the age of 10 yrs. (CFF guidelines. Moran & al 2010)
- OGTT is inconvenient, time consuming & difficult to comply with. (Walshaw & al)

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Background

- At the Graub CF center (SCMCI), prospective follow up with HbA_1c and extensive oral glucose tolerance test (OGTT) of CF patients with pancreatic insufficiency above the age of 10 years has been part of routine care for more than 2 decades.

- The routine OGTT included: glucose, insulin, c-peptide blood levels on fasting and 30,60, 90 & 120 minutes post glucose ingestion.

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Objectives

- To identify potential demographic, clinical, and laboratory predictors of the development of CFRD in patients with CF at the Graub CF center in SCMCI.

Definitions based on OGTT

- **Normal glucose tolerance (NGT)**:
  one hour plasma glucose (PG1)<200mg/dl & PG2<140mg/dl

- **Impaired glucose tolerance (IGT):**
  PG2 $\geq$ 140 and < 200 mg/dl

- **CFRD:**
  PG2 $\geq$ 200 mg/dl

- **CFRD with or without** Fasting Plasma Glucose(FPG)
  FPG $\geq$ 126 mg/dl

- **indeterminate glucose tolerance (INDENT):**
  Glucose levels $\geq$ 200 mg/dl at 30',60' or 90'

Moran & al. JCF 2013

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Methods and subjects

- Retrospective study of a prospective cohort
- Inclusion criteria:
  - Pancreatic insufficient CF patients over 10 years of age followed between years 1999-2013.
- Exclusion criteria:
  - Patients diagnosed with diabetes before 1st follow up.
  - Patients after lung or liver transplant

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Methods (cont.)

Data collected:

- Demographics, family history of diabetes, CF complications. Annual OGTT including glucose, insulin and C-peptide at 0, 30, 60, 90,120 minutes. FEV1, BMI,CRP & HbA1c
- The data was collected over 3 following years until the diagnosis of diabetes (CFRD group) **or** impaired glucose tolerance (IGT) group **or** the latest evaluation in the group with normal OGTT (NGT group)

Area under the curve (AUC) of glucose & homeostasis model assessment insulin resistance (HOMA-IR) were calculated.

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Statistics

- Findings were compared between patients who developed CFRD (CFRD group) and those with normal glucose tolerance and impaired glucose tolerance (NGT+IGT group)

- ANOVA test, T-test, chi-square test, and multiple regression analysis were used.

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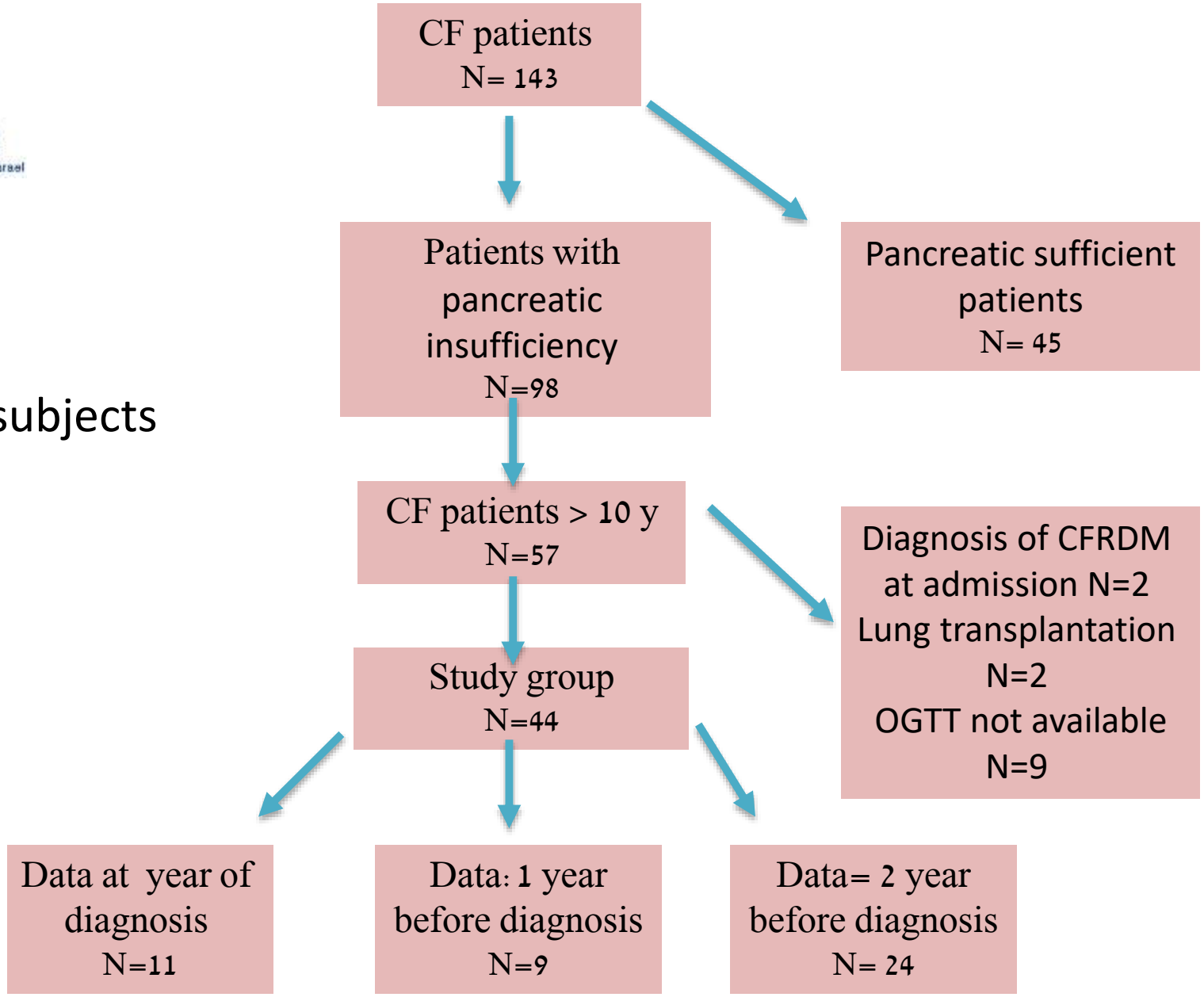
Study subjects



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Results

- Forty four patients were included, 16 patients developed CFRD
- The CFRD group (N=16) compared to the NGT+IGT group (n=28) had :
  - Higher (AUC) of glucose (P=0.003)
  - Higher glucose levels at **60' & 90'** after OGTT (P=0.017,0.003 respectively)
  - Higher HbA1c concentrations: 5.86±0.3 vs 5.54±0.4 (P=0.026)
  - HOMA-IR at diagnosis between the CFRD group and the (NGT+IGT) group yielded a significant between-group difference (0.95 and 1.78, respectively, P=0.021)

In multiple regression analysis we found that the most powerful predictor is **AUC of glucose**. Every rise of one unit of this variable predicts a **4% rise** in the chance of developing diabetes in two years

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Results

- Rate of liver disease was higher in pts with CFRD (62.5%) than in pts with NGT +IGT (28.6%),P=0.021
- No significant difference was found between the two groups regarding:
  - Family history of diabetes, BMI, FEV% predicted,
  - Levels of insulin, C-pepptide & CRP

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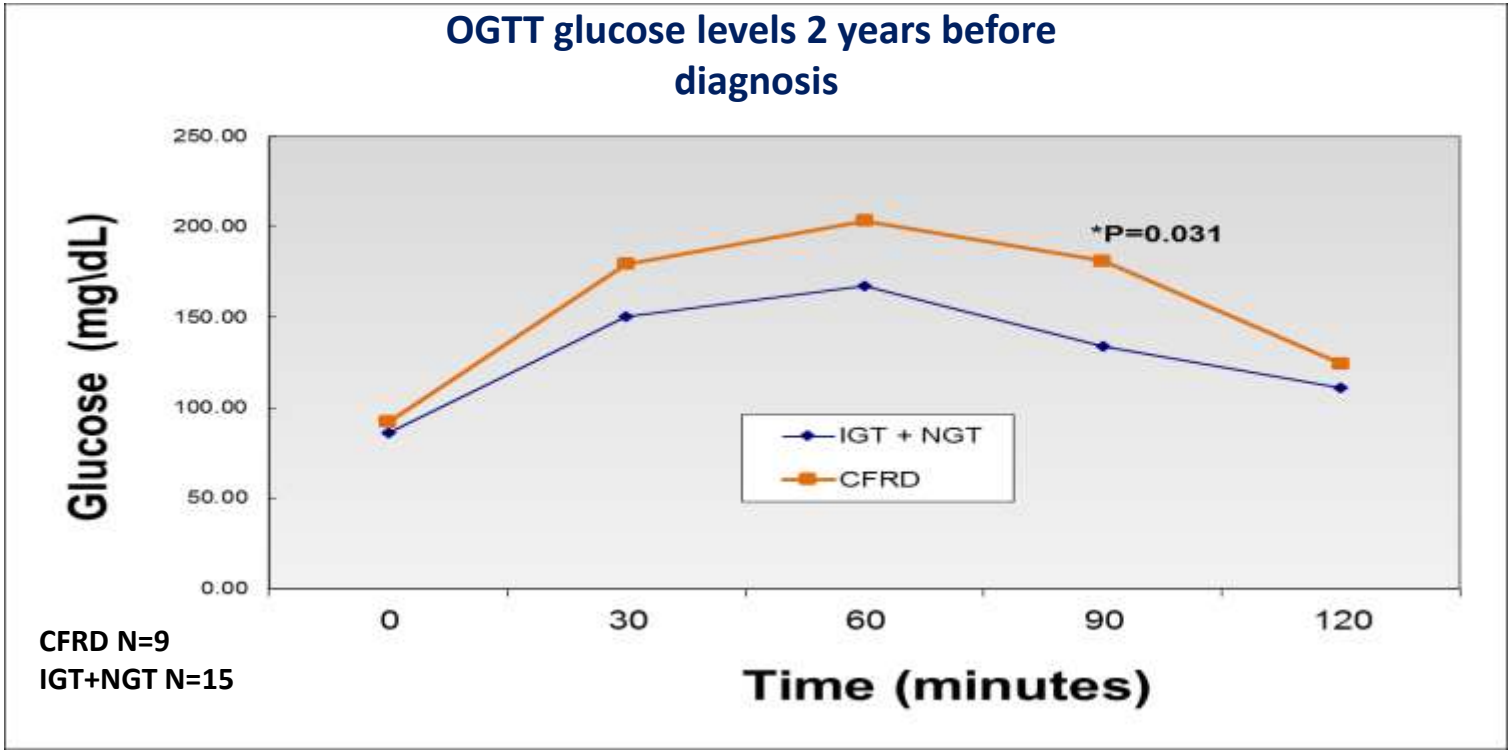
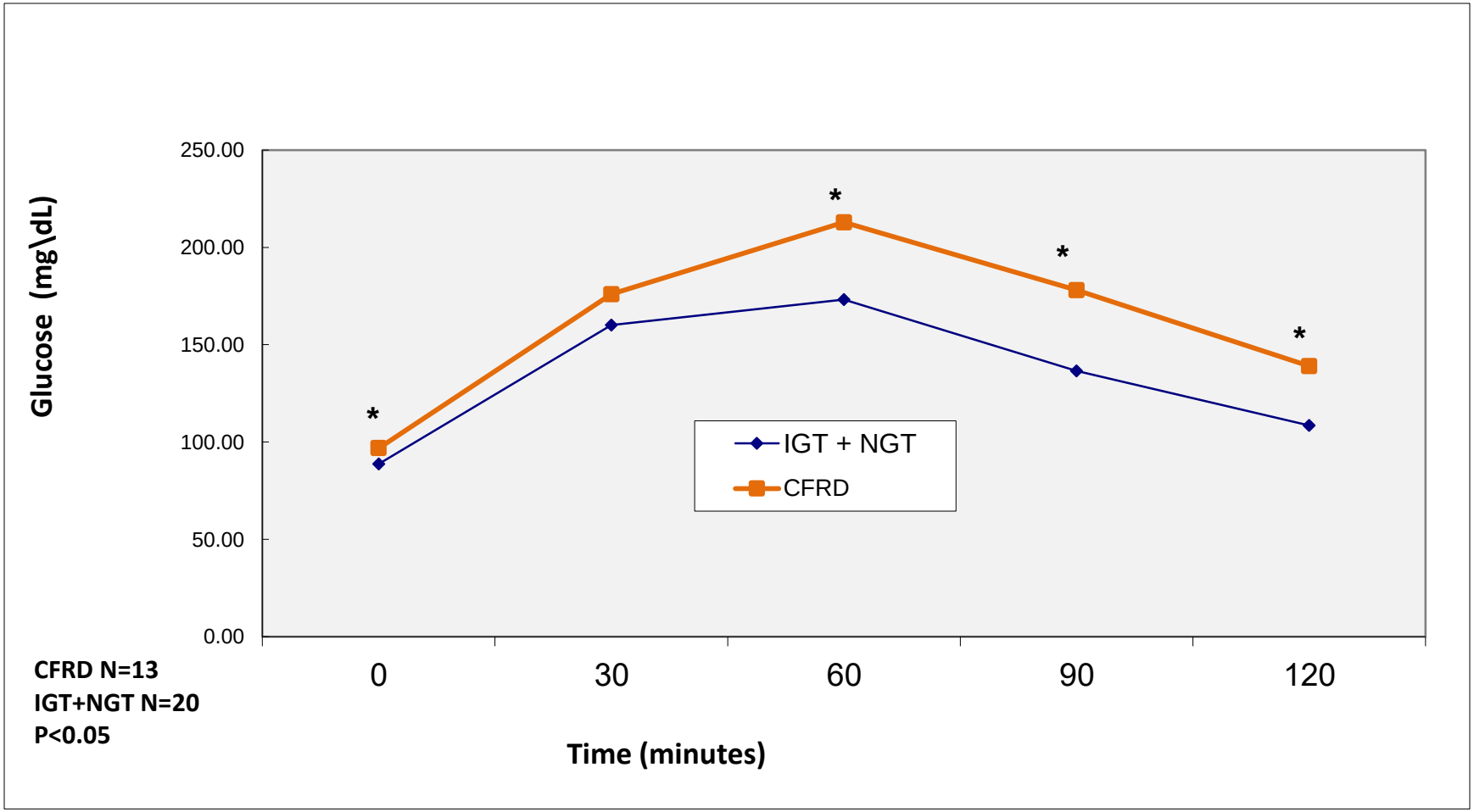
Results



OGTT glucose levels 1 year before diagnosis



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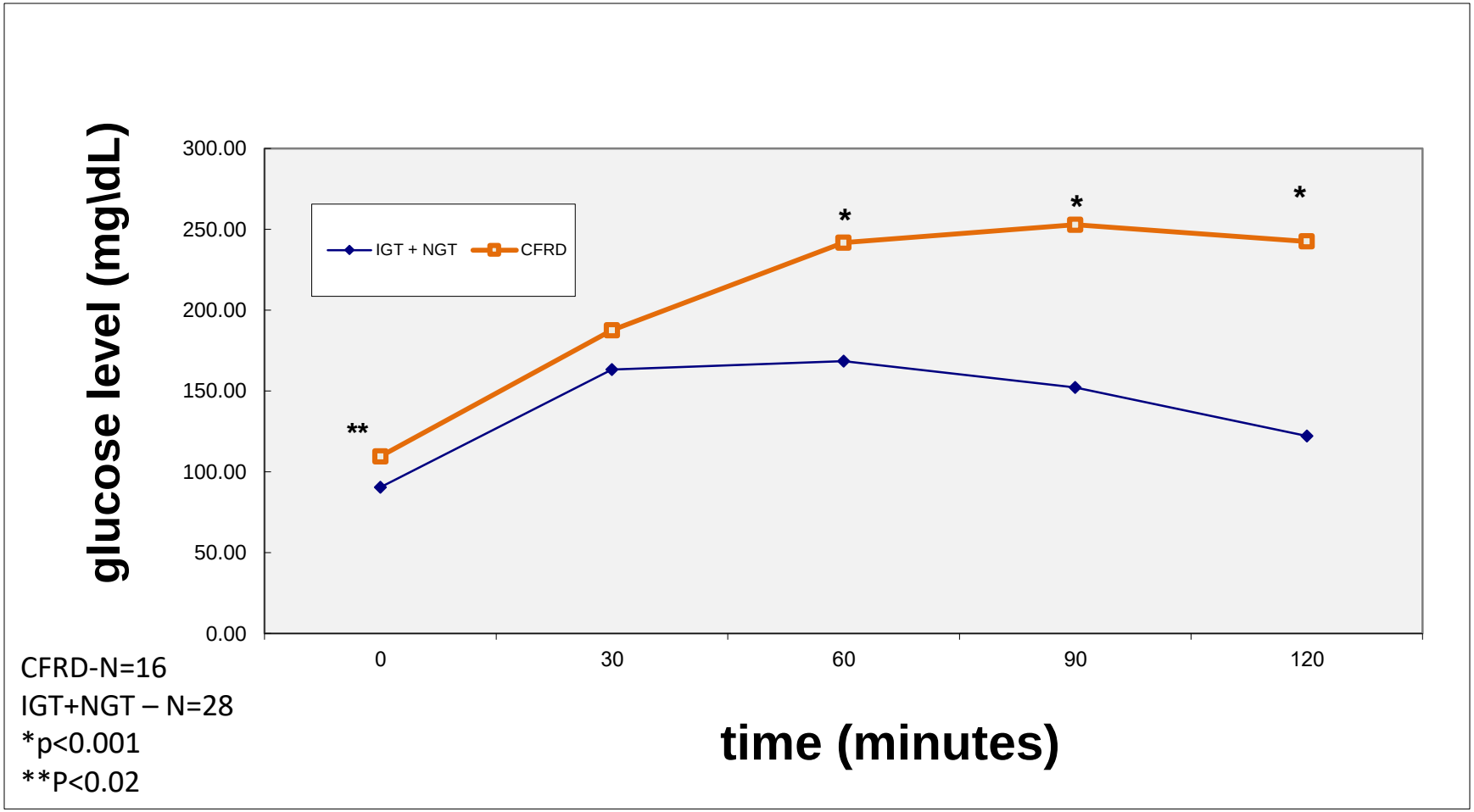
OGTT glucose levels at diagnosis



CFRD-N=16
IGT+NGT – N=28
*p<0.001
**P<0.02

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Discussion

- **HbA1C was significantly higher in the CFRD group**
- International guidelines recommend annual OGTT for all CF patients aged ≥ 10 years. This is controversial.
  - OGTT is inconvenient & time consuming.
  - The specificity & sensitivity of OGTT in CF has never been proven (Walshaw 2009).
- The need for an effective & easier screening tool to reduce the need for annual OGTT is needed.
- According to the CFF guidelines, HbA1C is considered unreliable in predicting CFRD
- Burgess & al (JCF 2015) conducted a validation study of 429 adult patients in predicting a positive OGTT.
  - HbA1c was the most discriminative: optimal threshold ≥ **5.8%** (40 mmol/mol); receiver operating curve (ROC) score (0.60)
  - The use of HbA1c ≥ 5.8% was found an effective tool for CFRD screening and reduced the need for an OGTT by 50.7%.

Burgess & al. JCF 2015

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Discussion

- High levels of glucose (≥ 200 mg/dl) at 60’ post glucose ingestion is defined by the guidelines for CFRD (2010) as indeterminate glucose tolerance (INDENT).

- Checking glucose levels at 60’ is not included in the recommended by the CFF guidelines

- INDENT was found as a significant predictor of CFRD development in a cohort of 1093 subjects (INDENT 119). (Schmidt & al 2013)

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Discussion

- Liver disease associated with CFRD development has been reported previously. (Moran & al 2005)

- In our study there was no sig. difference between the groups regarding BMI and FEV1
  - Low BMI & lower FEV1 was previously reported with CFRD (Moran & al 2005)
  - This could be due to the small cohort in our study

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limitations

- A retrospective cross sectional study design
- Small sample

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Conclusions

- AUC of glucose predict an increased risk of developing CFRD.
- Patients with HbA_1c values ≥ **5.8%** (40 mmol/mol) are in higher risk to develop CFRD & has to be followed closely
- High levels of glucose (≥ 200 mg/dl) at 60' post glucose ingestion (INDENT) can predict CFRD development
- CFRD is apparently not preceded by a significant decrease in insulin secretion. **Insulin resistance appears to be the major cause of CRFD.**
- Liver disease may be a risk factor of developing CFRD

Thank You!