

# Comorbidities and Transplantation

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## Comorbidities:

- Osteoporosis/osteopenia
- Diabetes
- BMI (obesity, overweight)
- Hypertension

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## Key Study Variables

- Comorbidities:
  - Osteoporosis/osteopenia
  - Diabetes
  - BMI (obesity, overweight)
- Outcome
  - HRQOL - health-related quality of life

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## Diabetes Mellitus

- Chronic metabolic disorder in which there is elevated level of glucose in blood
- Diagnosis is based on:
  - elevated fasting plasma glucose ( $\geq 126$  mg/dl)
  - elevated glucose with symptoms
  - or abnormal glucose tolerance test

(ADA, 2003)

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## Overweight/Obese (BMI)

- Classification BMI ( $\text{kg}/\text{m}^2$ )
  - Underweight  $< 18.5$
  - Normal  $18.5 - 24.9$
  - Overweight  $\geq 25.0$
  - Obese  $\geq 30.0$

(WHO, 2004)

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## Hypotheses

Directional Hypotheses:

- H1- The presence of osteoporosis at the time of lung transplant evaluation is negatively related to post-transplant health-related quality of life.
- H2- The presence of diabetes at the time of lung transplant evaluation is negatively related to post-transplant health-related quality of life.
- H3- Overweight status at the time of lung transplant evaluation is negatively related to post-transplant health-related quality of life.

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### Hypotheses

At the time of transplant evaluation, the presence of :

- osteoporosis
- diabetes
- overweight status

is negatively related to post-transplant health-related quality of life.

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### Methodology

- Descriptive analysis of existing data using statistical modeling
- Effect size (moderate;  $R^2 = .12$ )
  
- Power (.80)
  
- Level of significance (.05)

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### Sample Characteristics: N= 92

- Age Mean = 51 years (SD 12) = national average
- Gender
  - 37% female
  - 63% male (nationally 58% male UNOS, 2007)
- Race/Ethnicity
  - 92% Caucasian, 8% African American, 100% non-Hispanic
  - (Nationally 84% Caucasian)
- Disease Type
  - 37% obstructive, 63% non-obstructive
  - (Squier, 1995-34% obstructive, Lanuza, 2000- 57%obstructive)
- Time since transplant
  - Mean 41 months (SD 40)

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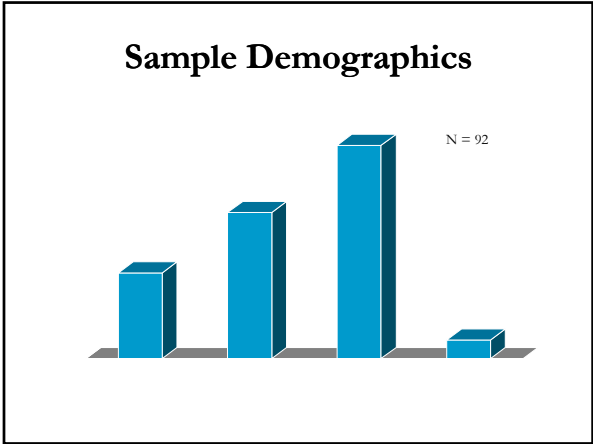
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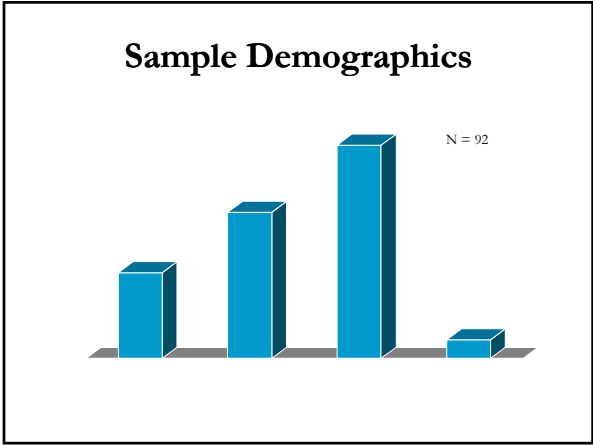
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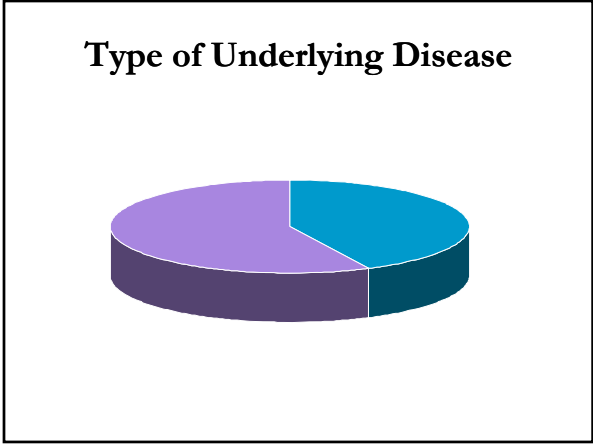
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## Results

- Bivariate Correlation coefficients
  - No moderate or large correlations among predictors (all  $r < 0.30$ )
  - Notable, statistically significant correlations between predictors and SF-36 Physical function scale were d BMI ( $r = -.297, p = xxx$ ) chronic rejection ( $r = -.286, p = xxx$ )

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Correlation matrix of predictors with outcomes

	Underlying Disease	Time since Txp	Evidence rejection	BMI	DM	osteoporosis
SF36 PCS	-.049	-.021	-.164	-.225	-.093	-.009
SF36 MCS	-.014	.026	.000	.000	-.120	-.022
SF-36 Physical Function	-.108	.086	<b>-.286</b>	<b>-.297</b>	-.079	-.004
SF-36 Role Physical	.015	.047	-.059	-.059	-.243	-.069
SF-36 Bodily Pain	-.077	-.164	-.047	-.047	.065	-.009
SF-36 General Health	-.076	-.088	-.098	-.098	-.115	-.064
SF-36 Vitality	.110	.013	-.018	-.018	-.140	.098
SF-36 Social function	.016	.082	-.067	-.067	-.114	.068
SF-36 Role emotional	-.112	.002	-.057	-.057	-.112	-.093
SF-36 Mental Health	-.056	.018	-.078	-.056	-.110	-.077

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## Results

- Block wise Multiple Regression
  - Physical component summary:
    - $p = .457$  [block 1],  $p = .287$  [block 2]
    - BMI neared statistical significance ( $p = .054$ )
  - Mental component summary:
    - $p = .994$  [block 1],  $p = .697$  [block 2]

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Model Physical Component Summary							
	R	R <sup>2</sup>	Std error	R square change	F change	Sig F change	Model significance
Block one	.170	.029	11.78	.029	.875	0.457	.457
Block two	.285	.081	11.66	.052	1.618	0.191	.287

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**Revised Model**

Revised Model –physical function as dependent variable

- $p = .012$  [block 1],  $p = .014$  [block 2]
- Coefficients
  - **Chronic rejection**  $B = -.286$   $p = .006$
  - **BMI**  $B = -.285$   $p = .007$

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Revised Model							
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## Results

■ Overweight BMI  $\geq 25.0$

■ **B = -.25** p = .03

■ Obese BMI  $\geq 30.0$

■ **B = -.23** p = .05

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Obesity/Overweight status

	Unstd $\beta$	Std error	STd $\beta$	Significance
(Constant)	66.59			
Underlying disease	-7.70			
Evidence Chronic Rejection	-18.48			
Time since transplant	0.10			
Indicator Overweight	-14.16		<b>.03</b>	
Indicator Obese	-16.37		<b>.05</b>	
Diabetes	-7.08			
Osteoporosis	-4.09			

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## Strengths & Limitations

■ **Strengths**

- Identified definition of HRQOL
- Sample Size
- Use of comorbidities as variables for study in this phenomenon

■ **Limitations**

- Retrospective, convenience sample
- Non-normal distribution
- Lack of pre-transplant HRQOL scores

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**Contributions to Science and Practice**

- Impact conceptual thinking re: HRQOL in the lung transplant population
- Identified overweight as an important variable
- Identified physical function as an important variable affected by comorbidities pre-transplant

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**Implications For Future Research**

- Use consistent HRQOL instruments
- Match Research question with domain specific HRQOL variables and outcomes
- Longitudinal prospective studies
- Larger, more diverse sample

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OSTEOPOROSIS

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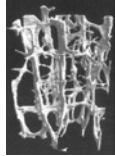
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## Osteoporosis



Normal Bone



Osteoporotic Bone

Old definition: a reduced amount of bone that is qualitatively normal

Modern definition: A systemic skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture.\*

\*Consensus Development Conference: Diagnosis, Prophylaxis, and Treatment of Osteoporosis. *Am J Med* 1991;90:107-110

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## Osteoporosis

### World Health Organization Criteria Postmenopausal Caucasian with DXA measure

Severe Osteoporosis  $\leq -2.5$  with Fracture

WHO Study Group [JBM](#) 1994

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## WHO Fracture Risk Prediction




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# DIABETES

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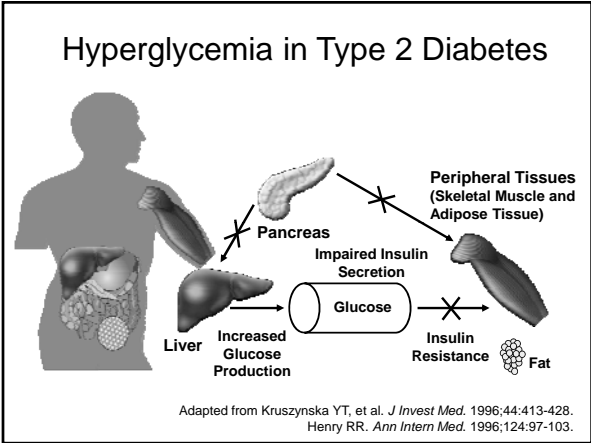
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### Definition of Diabetes

- **Diabetes Mellitus:**  
Heterogeneous Condition With Hyperglycemia and Common Complications
- **Insulin Deficiency:**  
Relative or Absolute

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## Risk Factors for Post Transplant Diabetes

Diabetes occurs post transplant at rate of:

9% at 3 months

16% at 12 months

24% at 36 months

Risk factors: Age >40-45, Obesity, AA and Hispanic Race, Family History, Hepatitis C and CMV, Polycystic kidneys

Post-transplant diabetes mellitus in renal transplant recipients. Tobin, G et al, UpToDate, May 31, 2008. UpToDate.com

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## Diabetogenic Factors and Screening for Diabetes

- Calcineurin Inhibitors → Reversible Islet Cell Toxicity, Sirolimus may be worst offender
- Glucocorticoids are Insulin Antagonists that → insulin resistance, hepatic glucose production and inhibit glucose transport into cells
- Screening for Diabetes:
  - Monitor blood sugar prior to transplant
  - Monitor blood sugar post transplant with FBS weekly X4, recheck in 3 months, 6 months and annually thereafter

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## Chronic Effects of Diabetes

- Large blood vessel disease → MI, stroke, peripheral artery disease and LE amputation
- Small vessel disease → retinopathy/vision loss and blindness, kidney damage/renal failure
- Neuropathy with pain, loss of protective sensation

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## Making the Diagnosis of Diabetes

Normo-glycemia	IFG or IGT	Diabetes
FPG < 100 mg/dl	FPG ≥ 100 and < 126 mg/dl (IFG)	FPG ≥ 126 mg/dl*
2-h PG < 140 mg/dl	2-h PG ≥ 140 and < 200 mg/dl (IGT)	2-h pp ≥ 200 mg/dl Symptoms of diabetes and random plasma glucose concentration ≥ 200 mg/dl

\*A diagnosis of diabetes must be confirmed on a subsequent day, by measurement of FPG, 2-h PG, or random plasma glucose (if symptoms are present).

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## New Diabetes

- Insulin resistant phenotype
- Usually requires some insulin
- May be possible to taper to oral agents
- May be possible to discontinue oral agents

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## Pre-existing Diabetes

- Type 1:
  - Steroids increase insulin requirement and dose
  - Insulin dose will increase from ESRD to having a working kidney
- Type 2
  - Cannot use all oral agents
  - Usually require insulin
  - Insulin and/or oral agent dose will increase from ESRD to having a working kidney

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# OBESITY

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**Overweight/Obese (BMI)**

- Classification BMI (kg/m<sup>2</sup>)
  - Underweight < 18.5
  - Normal 18.5 – 24.9
  - Overweight ≥25.0
  - Obese ≥30.0

(WHO, 2004)

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**BMI**

- Factors:
  - Sedentary lifestyle
  - Medication
    - steroids
- BMI 27 or greater assoc with higher risk  
= 5'6 " 167 lbs

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## Obesity

- Strategies to assist patients
  - Wean steroids as soon as possible
  - Pre-transplant counseling
  - Support groups
  - Others.....

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# HYPERTENSION

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## Hypertension

- defined as blood pressure >140/90 mmHg
- World Health Organization/International Society of **Hypertension** (>130/85 mmHg)
- since the introduction of calcineurin inhibitors, systemic **hypertension** is now found in transplant **70–90%** of transplant recipients

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## Hypertension

- Pre-transplant factors
  - Pre-existing hypertension and LVH
  - Body mass index
  - Primary kidney disease (native kidneys)
- Donor related
  - Hypertensive donor
  - Elderly and female donor
  - Hypertensive donor
- Transplantation related
  - Prolonged ischemia time
  - Delayed graft function

Nephrol Dial Transplant (2002) 17: 1166-1169

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### Hypertensive Agents

Agent Class	Pros	Cons
Non-dihydropyridine CCB	<ul style="list-style-type: none"> <li>■ Good for heart rate control</li> <li>■ May help CNI renal vasoconstriction</li> </ul>	<ul style="list-style-type: none"> <li>■ Drug interactions</li> <li>■ Bradycardia</li> <li>■ edema</li> </ul>
Dihydropyridine CCB	<ul style="list-style-type: none"> <li>■ Good tolerability</li> <li>■ May help CNI renal vasoconstriction</li> </ul>	<ul style="list-style-type: none"> <li>■ edema</li> </ul>
ACE-Inhibitors and ARBs	<ul style="list-style-type: none"> <li>■ Good for renal preservation and CV outcomes</li> <li>■ Good in diabetes patients</li> <li>■ Improves proteinuria</li> </ul>	<ul style="list-style-type: none"> <li>■ Increased creatinine</li> <li>■ Hyperkalemia</li> <li>■ cough</li> </ul>
Alpha/beta blockers (carvedilol, labetalol)	<ul style="list-style-type: none"> <li>■ Better BP reduction than beta blocker</li> <li>■ Carvedilol good for CHF</li> </ul>	<ul style="list-style-type: none"> <li>■ Hypotension/orthostasis</li> </ul>
Beta blockers	<ul style="list-style-type: none"> <li>■ Good in post-MI, CAD, CHF</li> </ul>	<ul style="list-style-type: none"> <li>■ Poor heart rate control in heart transplant</li> <li>■ Bradycardia</li> <li>■ fatigue</li> </ul>

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### Hypertensive Agents

Agent Class	Pros	Cons
Thiazide diuretics	<ul style="list-style-type: none"> <li>■ Well tolerated</li> <li>■ Good synergy with ACEI/ARB</li> </ul>	<ul style="list-style-type: none"> <li>■ Not effective in patients with GFR&lt;40-50</li> <li>■ hypokalemia</li> </ul>
Potassium sparing diuretics	<ul style="list-style-type: none"> <li>■ Useful in resistant hypertension</li> <li>■ Useful in advanced CHF</li> </ul>	<ul style="list-style-type: none"> <li>■ May cause hyperkalemia</li> <li>■ Gynecomastia (spironolactone)</li> </ul>
Loop diuretics	<ul style="list-style-type: none"> <li>■ Good volume control in CKD patients</li> <li>■ Useful in CHF</li> <li>■ Good natriuresis</li> </ul>	<ul style="list-style-type: none"> <li>■ Require BID dosing except torsemide</li> <li>■ Hypokalemia, volume depletion</li> <li>■ gout</li> </ul>
Vasodilators (hydralazine, minoxidil)	<ul style="list-style-type: none"> <li>■ Useful in refractory hypertension</li> <li>■ Useful in CHF</li> </ul>	<ul style="list-style-type: none"> <li>■ Reflex tachycardia</li> <li>■ Edema (requires loop diuretic)</li> </ul>
Central-acting agents (clonidine)	<ul style="list-style-type: none"> <li>■ Useful in refractory hypertension</li> <li>■ Patches are best</li> </ul>	<ul style="list-style-type: none"> <li>■ Fatigue</li> <li>■ Rebound hypertension</li> <li>■ Dry mouth</li> </ul>

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## Hypertension Pearls

- Consider common causes of refractory hypertension
  - NSAIDs, herbal supplements, alcohol
  - Nonadherence
  - Sleep apnea
  - Sodium intake
- consider calcineurin inhibitor toxicity (drug interactions- i.e. diltiazem/verapamil and cyclosporine)
- Patients often require loop diuretics to manage volume- make sure dose is adequate (BID dosing for furosemide and bumetanide)
- Watch the potassium!
- Consider renal artery stenosis- in renal transplant or in native renal arteries

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