COMPLICATIONS AFTER SOLID ORGAN TRANSPLANTATION

A. Perkowska-Ptasińska
Death causes among kidney transplant recipients

OPTN/UNOS DATA

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Howard RJ.; Transplantation 2002, 73, 1923
Malignancy after solid organ tx

- *de novo*
- recurrent malignancy
- (unintended) transmission from the donor
MAIN RISK FACTORS FOR POST Tx ONCOGENESIS

- recipient’s young age
- infections
- immunosuppression
- donor-recipient interactions associated with HLA Ah concordance and type of donation (cadaveric vs living-related)
Renal transplant recipients are approximately 4 times more likely to develop cancers than the general population.
Malignancy after solid organ tx

In comparison to general population malignancies in KTX recipients:

- occur at younger age
- have more aggressive course
- there is more common occurrence of multiple malignancies
- good HLA concordance and living-related donation are associated with lower risk of post Tx malignancy
The incidence of malignancy in KTX recipients (Australia/NZ)
Malignancy after solid organ tx

1. lip and skin carcinoma - 40%
2. non-Hodgkin lymphoma - 17%
3. urinary tract carcinoma - 3.4 - 9.9%
4. cervical ca *in situ* - 9%
5. Kaposi sarcoma - 5%
6. primary liver carcinoma - 3%
7. vulvar and anal carcinoma - 2.5%
The tumor sites with a five-fold or greater increase compared with the general population:

- Kaposi sarcoma (SIR 61 and EAR 15)
- skin (nonmelanoma, nonepithelial SIR 13.9 and EAR 22)
- non-Hodgkin lymphoma (SIR 7.5 and EAR 168)
- liver (SIR 11.6 and EAR 110)
- anus (SIR 5.8 and EAR 9.6)
- vulva (SIR 7.6 and EAR 6.5)
- lip (SIR 16.8 and EAR 16)

**SIR**: standardized incidence ratio
**EAR**: excess absolute risk
Other common malignancies with a statistically significant ($p<0.001$) increase included the following:

- lung (SIR 2.0 and EAR 85)
- kidney (SIR 4.7 and EAR 76)
- colon and rectum (SIR 1.2 and EAR 15.8)
- pancreas (SIR 1.5 and EAR 6.4)
- melanoma (SIR 2.4 and EAR 29)

SIR: standardized incidence ratio
excess absolute risk (EAR)
Malignancies with the same or lower incidence in transplant recipients population as in general population

1. breast cancer
2. prostate
3. lung cancer (with the exception of lung and heart transplant recipients)
4. ovarian carcinoma
Skin cancers

-account for almost 40 percent of malignancies in organ transplant recipients,
- develop in more than 50 percent of patients
- the most commonly reported skin cancers: squamous cell carcinoma (SCC), basal cell carcinoma (BCC), melanoma, and Kaposi’s sarcoma

MAIN RISK FACTORS:
1. immunosuppression:
   - reduced immune surveillance - facilitates the survival and proliferation of atypical cells
   - direct carcinogenic effects of immunosuppressive agents such as azathioprine or cyclosporine
   - proliferation of oncogenic viruses in the setting of immunosuppression

2. Ultraviolet radiation and fair phenotypic features
Lymphoproliferative disorders

- The wide spectrum of disorders ranging from reactive, polyclonal lymphoproliferations to lymphomas
- The majority are of B-cell origin, most commonly non-Hodgkin lymphoma, commonly associated with EBV infection
- T-cell lymphoproliferative disorders are rare, but have poorer prognosis
BOSNIAK CLASSIFICATION SYSTEM OF RENAL CYSTIC MASSES

Bosniak 1
- simple cyst, imperceptible wall, rounded, percentage malignant: ~0%

Bosniak 2
- minimally complex, a few thin (<1 mm) septa, thin calcifications; generally well marginated, percentage malignant: ~0%

Bosniak 2F
- minimally complex but requiring follow up, increased number of septa, thick calcifications, hyperdense cyst, percentage malignant: ~25%

Bosniak 3
- indeterminate, thick or multiple septations, mural nodule, percentage malignant: ~54%

Bosniak 4
- clearly malignant, solid mass with a large cystic or a necrotic component, percentage malignant: ~100%
RCC (renal cell carcinoma) is more common among kidney transplant recipients than in general population, particularly in those with acquired cystic kidney disease (ACKD).

Bosniak I and II cysts are considered benign.
Bosniak III and IV cysts are considered to have a high malignant potential.
A Bosniak IIF renal cyst cannot clearly be categorized and needs follow-up imaging.

- Independent of ACKD, all transplant patients should, at minimum, undergo ultrasonography of the native kidneys once a year.
- Patients with ACKD plus Bosniak category I or II cysts should undergo renal ultrasonography twice a year and CT scan for progressive lesions.
- Patients with ACKD plus Bosniak category IIF cysts should undergo renal ultrasonography four times per year and yearly CT scan or MR imaging. Nephrectomy and CT scan for progressive lesions should be performed if progression is observed, even if category III and IV cysts are not reached.
- Patients with ACKD plus Bosniak category III or IV cysts should undergo nephrectomy.
The ability to prevent and detect solid organ malignancies in the transplant patient, particularly early stage carcinomas, relies upon periodic screening examinations and strict adherence to prophylactic measures.

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<th>Cancer type</th>
<th>Recommendation</th>
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<tr>
<td>Breast</td>
<td>Women 50 to 69: annual screening mammography with or without clinical breast examination; age 40 to 49: the benefit of screening is less certain, and should be left to the decision of the physician and patient; ≥70 years of age: annual screening is appropriate as long as estimated life expectancy is ≥8 years.</td>
</tr>
<tr>
<td>Skin</td>
<td>Monthly self examination; physician examination annually, with early referral for suspected lesions.</td>
</tr>
<tr>
<td>Cervical</td>
<td>All women ≥18 years old and sexually active girls &lt;18 years old should undergo an annual pelvic examination and PAP smear.</td>
</tr>
<tr>
<td>KS/other sarcomas</td>
<td>Examination of skin, conjunctivae, and oropharyngeal mucosa annually; patients at higher risk (ethnicity, geographic area of residence or serologic positivity for HHV) may benefit from more frequent screening.</td>
</tr>
<tr>
<td>Prostate</td>
<td>Annual screening with digital rectal examination and PSA recommended for men ≥age 50, if their estimated life expectancy is at least 10 years. If positive family history or African American race, may start annual screening earlier (eg, age 45).</td>
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<td>Colorectal</td>
<td>Starting at age 50: annual FOBT and either sigmoidoscopy every five years or colonoscopy every 10 years.</td>
</tr>
<tr>
<td>HCC</td>
<td>For patients with chronic hepatitis B or C and cirrhosis, serum AFP and liver ultrasound every 6 to 12 months. Serum AFP has a low sensitivity for the detection of small hepatocellular carcinomas (HCCs) (ranging between 20 to 60 percent), but high specificity (exceeding 90 percent in most series). Hepatic US is more sensitive than serum alpha-fetoprotein (exceeding 80 to 85 percent for the detection of small HCCs ranging in size from 1 to 5 cm). Suspicious lesions should be evaluated with contrast-enhanced CT.</td>
</tr>
<tr>
<td>Renal cell</td>
<td>Screening via cytologic or radiographic means is not recommended, except possibly for patients with a history of analgesic abuse.</td>
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The role of immunosuppression in oncogenesis

- DNA injury/inhibition of DNA repair
- Defected immunoregulation
- Promotion of chronic viral infections with EBV, HBV, HCV, HHV 8, HPV
- ATG/OKT3 increases the risk of PTLD.
- Decreased number of CD4 T cells increases the risk of skin cancer
- The risk of malignancy is related to immunosuppressants' dosages

The overall level of immunosuppression appears to be the principal factor that increases the risk of posttransplant malignancy.
Reduction of immunosuppressive therapy in recipients with active malignancy

- Reduction or cessation of immunosuppressive therapy is useful **ONLY** for renal and/or pancreas transplant recipients, since loss of the graft to rejection is not a fatal event in these patients. Reduction or cessation of immunosuppressive therapy may result in tumor regression in some cases of lymphoma, some skin cancers KS, and donor-derived malignancies.

- In other solid organs recipients you **CANNOT** withdraw immunosuppression since patients' life depends on graft function.
ANTIMETABOLITES

MYCOPHENOLATE MOFETIL

- **impairs lymphocyte function by blocking purine biosynthesis via inhibition of the enzyme inosine monophosphate dehydrogenase. Some malignancies have dramatic elevations of this enzyme, suggesting that this agent may have some antiproliferative activity**
- **A principal mechanism of a lower malignancy risk with mycophenolate mofetil may be due to the decreased incidence of acute rejection. This results in a reduced need for increased doses of immunosuppressive agents.**

AZATHIOPRINE

- **the use of Aza has been associated with neoplastic development post-Tx, particularly an increased risk of cutaneous squamous cell carcinomas. The postulated mechanism of action: inhibition of repair splicing and induction of codon misreads via intercalation of DNA**
CALCINEURINE INHIBITORS

• there is a dose-dependent relationship between calcineurin inhibitors and secondary malignancies
• cyclosporine exerts proangiogenic effect due to elevated expression of vascular endothelial growth factor (VEGF)
• cyclosporine increases levels of interleukin-6, which may help EBV-induced B cell growth
• cyclosporine and tacrolimus may promote cancer progression, principally via the production of transforming growth factor-beta (TGF-beta).
• tacrolimus in lower dosages induces apoptosis and does not increase the risk of oncogenesis
- ATG, OKT-3; lymphocytes T depletion → PTLD, skin carcinoma
- Rituximab; lymphocytes B depletion: may reduce the incidence of lymphoproliferative disorders and is regarded by many as appropriate first line therapy for these disorders
PROLIFERATION SIGNAL INHIBITORS

Sirolimus i Everolimus;
- inhibition of protein mTOR → direct inhibition of growth and proliferation of cells, including neoplastic cells
- decreased VEGF production → inhibition of angiogenesis,
- promotion of apoptosis,
- inhibition of lymphocytes T activation,
- limitation of cell migration and invasiveness

Neoplastic tissue regression with sustained immunosuppressive effect
Skin malignancies and PSI

A

First Skin Carcinoma (% Patients)

 protocol extension to 60 months

 Protocol Extension to 60 Months

 Amendment to Discontinue SRL-CsA-ST Patients

Log-Rank Test, \( p = 0.459 \)

\[ \text{SRL-CsA-ST} \]

\[ \text{SRL-ST} \]

Randomization

\[ * \text{SRL-CsA-ST vs SRL-ST} \]

Months

B

Skin Carcinoma (events)

 protocol extension to 60 months

 Protocol Extension to 60 Months

 Amendment to Discontinue SRL-CsA-ST Patients

Relative Risk* = 0.346

\( p < 0.001 \)

\[ \text{SRL-CsA-ST} \]

\[ \text{SRL-ST} \]

Randomization

\[ * \text{SRL-ST to SRL-CsA-ST} \]

Months

*Campistol JM i wsp Journal Am Soc Nephrol 2005*
The impact of viral infections on oncogenesis

Oncogenic viruses: disturb pathways that regulate cells proliferation, inactivate tumor suppressor genes

- **EBV** – PTLD
- **HBV, HCV** – HCC (hepatocellular Ca)
- **HTLV 1** – T cell leukemia
- **HPV** – Ca of cervix and anogenital region
- **HPV 58** – Bowen’s Ca
- **HPV 8, 9** – skin Ca
- **HPV 16, 20** – tonsillar Ca, skin Ca
- **HHV 8** – Kaposi Sa
Recommendations:

The impact of a history of malignancy on patient management is determined by the availability of alternative management approaches.
Recommendations for kidney Tx

No waiting period for transplantation is necessary with low-risk tumors:
- low stage renal carcinoma,
- *in situ* carcinoma,
- primary basal cell skin carcinoma,
- low-grade bladder cancer.

Transplantation should be delayed for at least five years with tumors that carry a high risk of recurrence following transplantation:
- melanoma (some recommend 10 years)
- breast cancer
- colorectal cancer

Transplantation should be delayed for approximately two years with most other tumors.
Incidence of malignancy reoccurrence after KTX

Incidence 0 - 10%
- low stage renal carcinoma
- lymphomas
- testicular, cervical, thyroid carcinoma

Incidence 11 - 25%
- uterine, colon, prostate, breast carcinoma
- Wilms tumor

Incidence > 25%
- bladder ca,
- skin ca
- sarcomas
- myeloma
- advanced renal carcinoma

NDT 2000, 15 supplement 7
Liver transplantation has been used to treat hepatocellular carcinoma when disease is localized to the liver

**Risk factors of HCC recurrence after OLTx:**

- the size of the tumor
- the number of malignant lesions and their localization
- the presence of metastasis to lymph nodes
- histological staging
- tumor angioinvasion
- tumor volume and AFP concentration
Milan and UCSF criteria for liver Tx as a treatment of HCC

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<th>MILAN CRITERIA</th>
<th>UCSF CRITERIA</th>
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<tr>
<td></td>
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<td>(Univ. Calif. in San Francisco)</td>
</tr>
<tr>
<td>Single lesion diameter (cm)</td>
<td>$\leq 5$</td>
<td>$\leq 6.5$</td>
</tr>
<tr>
<td>Multiple lesions - number</td>
<td>$\leq 3$</td>
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</tr>
<tr>
<td>Largest tumor diameter if multiple (cm)</td>
<td>$\leq 3$</td>
<td>$\leq 4.5$</td>
</tr>
<tr>
<td>Total tumor diameter if multiple (cm)</td>
<td></td>
<td>$\leq 8.5$</td>
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Transmission of malignant cells from a donor is rare, but may result in metastatic cancer in the immunosuppressed transplant recipient.

**Table 5.** Organ-specific incidence of donor tumor transmission to transplant recipients: UNOS, 4/1/94-12/31/00

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<th>Organ</th>
<th>Transmission Number (%)</th>
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<td>Liver (n=27,910)</td>
<td>7 (0.025%)</td>
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<tr>
<td>Kidney (n=52,539)</td>
<td>3 (0.006%)</td>
</tr>
<tr>
<td>Heart (n=15,379)</td>
<td>2 (0.013%)</td>
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The only types of donor’s malignancies considered safe (no risk of transmission) are:

- basal cell carcinoma of the skin
- cervical ca *in situ*
- some of primary OUN malignancies (grade <III)
Malignancies that definitely exclude the donation:

- melanoma
- breast cancer
- sarcomas
- chorioncarcinoma
- grade III or IV primary OUN malignancies
History of malignancy in potential recipient

If malignancy is considered cured, it does not constitute a contraindication to Tx.
SUMMARY AND RECOMMENDATIONS

• There is an increased risk of a wide range of cancers in recipients solid organ transplantation. The incidence of specific malignancies appears to vary depending upon the organ transplanted.
• Several factors have been linked to the increased incidence of secondary malignancies after solid organ Tx including sun exposure, the extent and duration of immunosuppression, and concomitant viral infections.
• In KTX recipients ACKD and pretransplantation dialysis increase the risk or native kidneys RCC.
• Sirolimus may confer a decreased risk of malignancy.
• Exposure to ATG increases risk of post-transplant lymphoproliferation
• At least four viruses may be carcinogenic in transplanted patients, including Epstein-Barr virus (EBV), HHV-8, human papillomavirus (HPV), and the Merkel cell polyomavirus (MCV).
• Unintended transmission of malignant cells from a donor is rare, but may result in metastatic cancer in the immunosuppressed transplant recipient.
• Reduction or cessation of immunosuppressive therapy is useful primarily for patients who have undergone renal transplantation, since loss of the graft to rejection is not a fatal event in these patients. Such measures may result in tumor regression in lymphoma, skin cancers, Kaposi’s sarcoma, and donor-derived malignancies.
Death causes among kidney transplant recipients

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Howard RJ.; Transplantation 2002, 73, 1923
The importance of cardiovascular complications in KTX recipients

- The risk of occurrence $5\times\uparrow$ than in general population

- Death with functioning graft - main cause of transplant loss

- Cardiovascular complications - main death cause among KTX recipients
Cardiovascular risk factors after KTX
typical of general population / typical of KTX recipients

- diabetes
- HT
- dyslipidemia
- left ventricular hypertrophy
- nicotinism
- hyperhomocysteinemia
- obesity
- sedentary lifestyle
- age
- male sex

- uremia before dialysis
- dialysis
- hyperparathyroidism
- cardiovascular disease before Tx
- IS (Pred, CsA, Tac, Rapa)
- anemia
- kidney graft insufficiency*
- proteinuria
- infections?
- thrombophilia?

* Meier-Kriesche, Transplantation 2003
Diabetes as a risk factor for ischemic heart disease

- In general population (Framingham Study)
  - RR in men 1.53
  - RR in women 1.82
- In KTX recipients > 1 year after Tx
  - RR in men 2.78
  - RR in women 5.4

New-onset diabetes after transplantation (NODAT)

- Diabetes most commonly develops within the first few months post transplant, although there is continued risk for the life of the patient and allograft.

- Hyperglycemia is dependant on type and dosage of diabetogenic drugs:
  - IS regimen may be altered or reduced to minimize the risks of diabetic complications;
  - if not, oral agents or insulin regimens will need to be implemented to properly control glucose levels;
  - steroids, calcineurin inhibitors and MTOR inhibitors can adversely affect blood glucose levels.

- Reasons for relatively high incidence of NODAT include the following:
  - the new kidney metabolizes and excretes insulin more efficiently than the failing native kidneys;
  - the transplanted kidney is gluconeogenic;
  - the immunosuppression regimen is diabetogenic;
  - pre-existing risk factors (such as genetic risk factors or metabolic syndrome) predispose patients to developing diabetes.

- NODAT is a risk factor for:
  - graft loss
  - recipient death
  - cardiovascular post-Tx complications
NODAT - risk factors

- increased age \(^1, 2, 6\)
- non-caucasian race \(^1, 6\)
- IS regimen
  - MP pulses as anti-rejection treatment \(^1, 2, 4\)
  - High dosages of CsA or tac \(^1\)
  - High pred dosage \(^2\)
- family history of diabetes \(^2\)
- HCV infection \(^3, 4, 6\)
- CMV infection \(^2\)
- obesity \(^3, 6\)
- the number of HLA mismatches \(^6\)
- HLA B 27 \(^2\)
- male donor \(^6\)

ADA criteria for diagnosing diabetes mellitus

- **IGT: IMPAIRED FASTING GLUCOSE:**
  fasting plasma glucose: 110 – 126 mg/dl and > 140 mg/dl in oral glucose tolerance test (OGTT)

- **DIABETES:**
  - signs (polyuria, polydypsia, weight loss) + random blood glucose level > 200 mg/dl
  - fasting plasma glucose > 126 mg/dl or a 2-hour post load glucose ≥ 200 mg/dl in OGTT

- **IFG: IMPAIRED FASTING GLUCOSE**
  fasting glycemia 110 mg/dl – 126 mg/dl and < 140 mg/dl in OGTT

*International Consensus Guidelines, Transplantation 2003*
Prophylaxis and treatment of NODM

• fasting plasma glucose min. 1x/week. for 4 weeks after Tx, subsequently in the 3., 6., 12., months,

• random plasma glucose every 12 months

• OGTT in pts with proper fasting glycemia and in those with fasting glycemia of 110-126 mg/dl

• IS modification:
  • GS minimalization or withdrawal
  • MMF, Aza, Rapa do not disturb glucose metabolism
Monitorig of recipients with diabetes

- **Glycemia control**
- **Serum lipids** – recommended concentrations:
  - LDL-chol < 100 mg/dl
  - HDL-chol > 40 mg/dl
  - TG < 150 mg/dl
- **HbA1C every 3 months**, recommended < 6.5 - 7%
- **BP recommended** < 130/80-85 mmHg
Treatment of Diabetes Mellitus in Transplantation Patients
(Various Therapeutic Options)

Elevated FPG
Meets ADA Criteria for Diabetes

Nutritional Counseling
FPG Monitoring
Lifestyle Modification

Type I Diabetes
Insulin

Type II Diabetes

Mean FPG < 300 mg/dl
Mean FPG > 300 mg/dl

Liver Function
Abnormal

Insulin

CrCl < 50 ml/min

Renal Function

Insulin Sensitizer (Rosiglitazone Pioglitazone)
or Insulin Secretogogue (Repaglinide)

Insulin Sensitizer (Rosiglitazone Pioglitazone)
or Insulin Secretogogue (Repaglinide)
or Sulfonylurea (Glibizide) and/or Metformin

Treatment of Diabetes Mellitus in Transplantation Patients
(Gauging Therapeutic Efficacy by HbA1c and FPG)

Untreated Patient

HbA1c < 7%
Monitor

HbA1c > 7%
Treat

Monotherapy
Insulin Sensitizer (Rosiglitazone, Pioglitazone)
or
Insulin Secretagogue (Repaglinide)
or
Sulfonylurea (Glibizide, Glyburide, Glyciprimide)

Target not met
HbA1c > 7%
FPG > 126 mg/dl

Dual Therapy
Insulin Secretagogue and Insulin Sensitizer or
Metformin
or
Sulfonylurea and Insulin Sensitizer or
Metformin

Target not met
HbA1c > 7%
FPG > 126 mg/dl

OR

Triple Therapy
Sulfonylurea and Insulin Sensitizer and
Metformin
or
Insulin Secretagogue and Insulin Sensitizer and
Metformin

Target not met
HbA1c > 7%
FPG > 126 mg/dl

Insulin ±
Insulin Sensitizer or
Metformin

Post tx hypertension

- incidence: 85-90%
- reasons:
  - chronic kidney graft disfunction
  - IS treatment (CIN, GS)
  - delayed graft function (DGF) due to post Tx ATN
  - transplant glomerulopathy (recurrent, or e novo)
  - renal artery stenosis
  - hemolytic-uremic syndrome (HUS)
  - the presence of native kidneys
  - HT before Tx
  - erythrocytosis (polycythemia)
  - hypercalcemia
  - cadaveric donation especially if donor had HT
The influence of IS drugs on post-Tx hypertension

- **CIN**: ↑ in vascular resistance due to:
  - sympathetic activation
  - functional supremacy of vasopressors (endothelin) over vasodilators (PGI, NO)
  - RAA activation

- **GS**: hypervolemia  
  (Zeier, Nephron 1998)

MMF, Aza, sirolimus do not cause hypertension
HT - treatment

AIM:
- in recipients with no proteinuria < 130/85 mmHg
- in recipients with proteinuria < 125/75 mmHg
- in immediate post Tx period < 160/90 mmHg

TOOLS:
- non-pharmacological: restricted salt diet, physical exercise, ↓body mass
- pharmacological
- IS modification
- bilateral nephrectomy (native kidneys)
HT - pharmacological treatment

- in recipients with no proteinuria - calcium channel blockers
- in recipients with proteinuria - ACE-I, ARB (angiotensin receptor blockers)
  - after exclusion of renal artery stenosis
  - potassium, Hb, crea control
- β-blockers, diuretics, α1-adrenolytics,

ACE-I, ARB - better BP control than with other hypotensive drugs

Stigant, Am. J. Kidney Dis. 2001
Renal artery stenosis in KTX recipients

- incidence: 2-6.6% (*Rengel Kidney Int 1998*)
- diagnostics:
  - doppler ultrasonography:
    lumen reduction > 50% + peak systolic velocity of > 2.5 m/sek, sensitivity 100%, specificity 95% (*Baxter, Clin. Radiol. 1995*)
  - NMR angiography: sensitivity and specificity of 100% (*Johnson Mag. Reson. Imaging 1997*)
  - arteriography
  - spiral CT
Renal artery stenosis - treatment

- Angioplasty without stenting
  - restenosis risk - 20%
- Angioplasty with stenting
  - 100% effective
- Surgery
  - indications:
    - resistant HT
    - atherosclerotic narrowing of recipient’s artery
  - disadvantages:
    - graft loss risk - 30%
    - restenosis risk - 10%
Post-KTx polycythemia

• incidence: 10-20% *Kasiske J. Am. Soc. Nephrol. 2000*

• pathogenesis:
  - ↑ erythropoietin synthesis (EPO) in renal transplant and in native kidneys
  - ↑ sensitivity of erythrocyte precursors to EPO
  - ↑ IGF-1 effects

• treatment: ACE-I, ARA, teophiline, krwioupusty
Left ventricular hypertrophy (LVH)

- incidence: 75% before Tx, 52% after Tx
  
  Ferreira, Transplantation 2002

- LVH regression after Tx:
  - ACE-i > diuretics

  Foley, Am. J. Kidney Dis. 1998
Dyslipidemia in KTX recipient

- **Types of disturbances and their incidence:**
  - Tchol > 240 mg/dl - 63%
  - LDL-chol > 130 mg/dl - 60%
  - HDL-chol < 35 mg/dl - 12%
  - TG > 200 mg/dl - 36% *Kasiske Semin. Nephrol. 2000*
  - Lpa > 30 mg/dl - 23% *Kasiske J. Am. Soc. Nephrol. 2000*

- **Qualitative disturbances** in lipoprotein content:
  - ↑ LDL susceptibility to oxidation,
  - ↑ LDL atherogenicity

- **CsA withdrawal** → ↓ LDL oxidation
  *Fellström, Transplantation 2000*
Immunosuppression and Hyperlipidemia Post Transplantation

GS:
- ↑ TG synthesis in liver,
- ↓ plasma lipoprotein lipase
- ↓ LDL receptor activity
- ↑ HMG-CoA reductase,
- ↓ ACTH,
- Insulin resistance,
- ↑ glu

CsA, tac:
- impaired LDL-chol binding in the liver
- ↓ bile acids (↓ 26-hydroksylazy),
- ↑ Lp(a)


Rapa:
- ↑ lipoprotein synthesis?,
- ↓ lipids clearance?,
- ↓ lipoprotein lipase?

Chueh, Transplantation 2003

MMF, Aza – do not affect lipids metabolism
IS modification in dyslipidemia – be aware of rejection risk!!!

- CsA → Tac  
  (Kohnle, Transplant. Int. 2000)
- ↓ GS dosage
- GS withdrawal (Hrick, Transplantation 1992)
  - positive effect: ↓ LDL-chol, ↓ TG
  - negative effect: ↓ HDL-chol, ↑ rejection risk
- Avoid rapa in pts with severe hyperlipidemia
- rapa → Tac
- rapa → MMF
- ↓ dosage/withdrawal of CsA
Hyperhomocysteinemia

- Definition: Hcy > 10 μmol/l
- ↓ vit. B6, B12, folic acid → ↑ Hcy
- ↑ crea → ↑ Hcy
- CsA, Tac → ↑ Hcy
- ↑ Hcy → ↑ cardiovascular risk in both general population and among KTX recipients
  

- vit. B6, B12, folic acid supplementation → Hcy → affects cardiovascular risk?
  
Nicotinism

• Incidence in Poland: 35-40%
• consequences:
  increased risk of cardiovascular complications and graft loss

Hageman, Cl. Transplant. 1995
Obesity

• definition: BMI > 30 kg/m²
• incidence: 40% KTX recipients in the 1st post Tx year


• consequences:
  - increased risk of cardiovascular complications
    Abate, Am. J. Med. 1999
  - increased risk of graft loss
    Modlin, Transplantation 1997
  - disturbed wounds healing
Cardiovascular risk modification – general rules

• detection and treatment of cardiovascular diseases before Tx
• high risk pts – pre Tx revascularization
• pts with the history of stroke or TIA – temporary (6 months) disqualification from Tx
• pts with high cardiovascular risk – aspirin after Tx
• modification of cardiovascular risk after Tx