Surgery and transplantation in the obese renal failure patient

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Aspects to consider

- The size of the problem
- Impact of obesity on:
  - Dialysis access
  - Renal transplantation
- Interventions

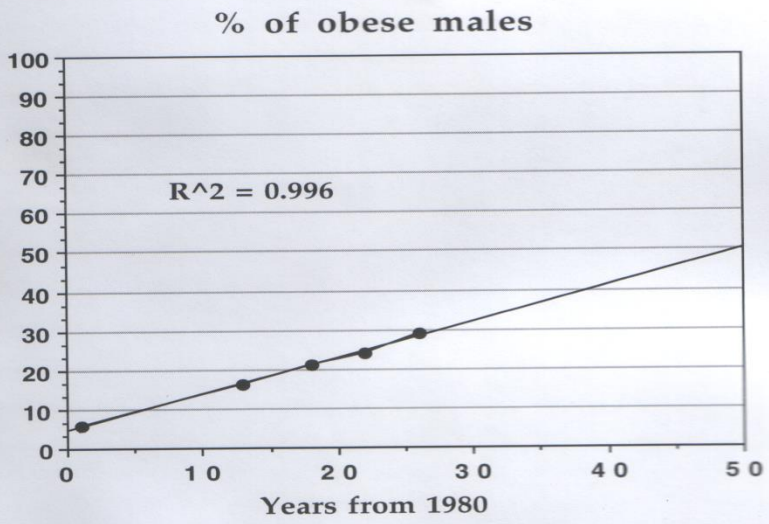
Definitions

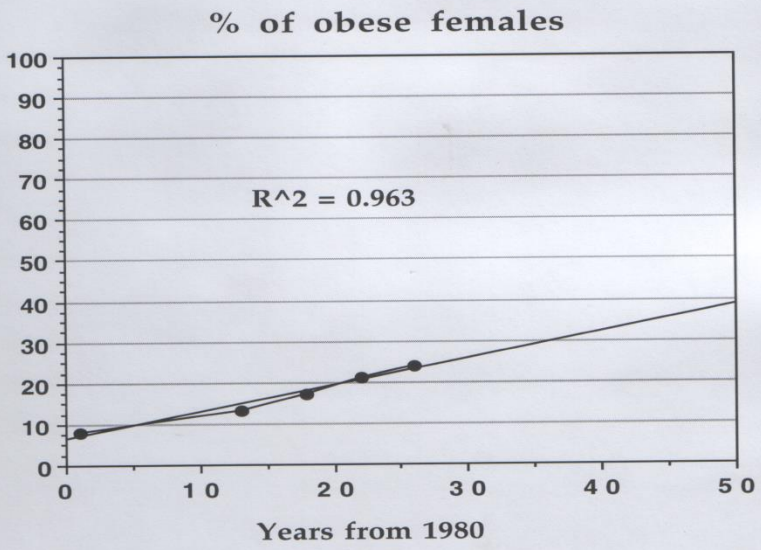
Classification by Body Mass Index (BMI; kg/m^2)

<18	underweight
18-25	desirable
27-30	overweight
30-35	obese
35-40 with med problems or >40	morbidly obese
>50	superobese

Obesity Related Comorbidity

- **Diabetes mellitus**
- **Hypertension**
- **Dyslipidaemia**
- **Hypoventilation syndromes (OHS and OSA)**
- Abdominal wall hernias including incisional hernia
- Some cancers – uterus, ovary, cervix, colon, prostate, lower oesophagus
- Asthma
- Gastro-oesophageal Reflux
- Gallstones
- NAFLD
- Osteoarthritis
- Neurological disorders
- Androgenisation, polycystic ovaries and infertility
- Psoriasis
- Venous stasis and varicose veins
- Affective disorders


% of obese males
R^2 = 0.996
100
90
80
70
60
50
40
30
20
10
0
0
10
20
30
40
50
Years from 1980

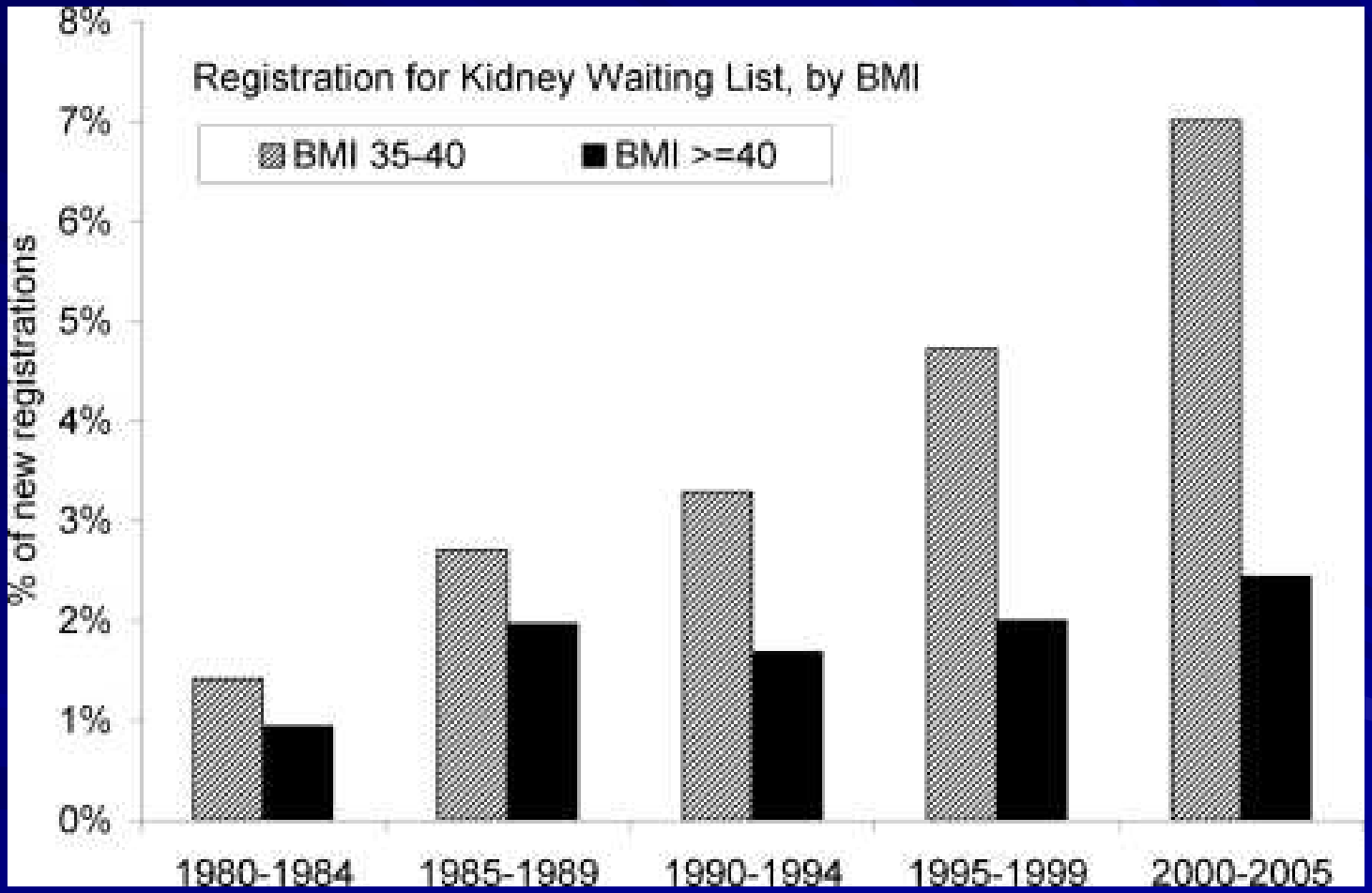

% of obese females
R^2 = 0.963
100
90
80
70
60
50
40
30
20
10
0
0
10
20
30
40
50
Years from 1980

Even our dogs are getting fatter

Obesity by proxy

		Dog owners	
		normal wt	obese
Dog	normal wt	75%	44%
	obese	25%	56%

Impact of obesity on renal transplantation – the obesity epidemic



Issues with ESRD and dialysis access in the obese

Obese patient have improved patient survival on dialysis

BUT

Obesity has a negative impact on progression of renal failure; earlier progression to ESRF

Impact on dialysis access
Primary access

- Lower rates of fistula versus graft for primary access
- Higher primary fistula failure (65 vs 45%)
- (Primary access failure = failure of an access to ever achieve adequacy for dialysis)

- Miller PE et al. Kid Int 1999; 56, 275-280

Impact on dialysis access

Improving primary access

- Primary fistula rates improved and primary access failure reduced by US guided vascular mapping
  - Identify artery > 2.0mm
  - Identify vein> 2.5mm
  - Exclude proximal venous stenosis
  - Postop Doppler to ensure:
    - Diameter>4mm, Flow > 500ml/min, depth <5mm
    - Consider intervention if too deep:

Impact on dialysis access – Secondary access survival

- Secondary access survival less good in the obese
- (secondary access failure = permanent failure of an access which had achieved adequacy for dialysis)
- BMI>30 versus BMI<30:

68 % versus 92% at 1 year

59 % versus 78% at 2 years

47 % versus 70% at 3 years

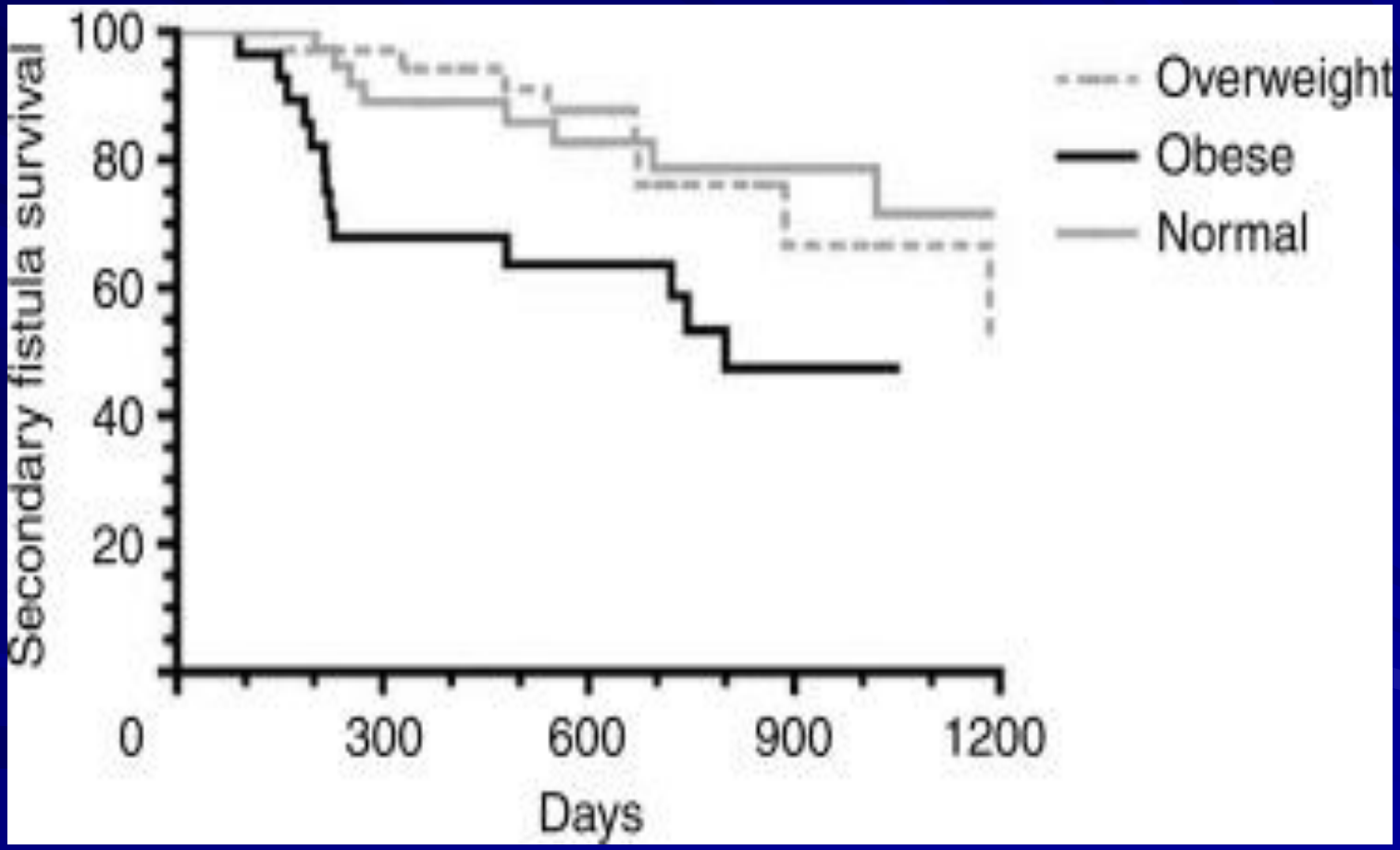
(HR 2.74, p=0.004)

MVA: Age, sex, race, diabetes, CAD, PVD, fistula location, BMI

Only BMI was significant factor in predicting access failure

Kats, m et al. Kid Int 2007; 71, 39-43

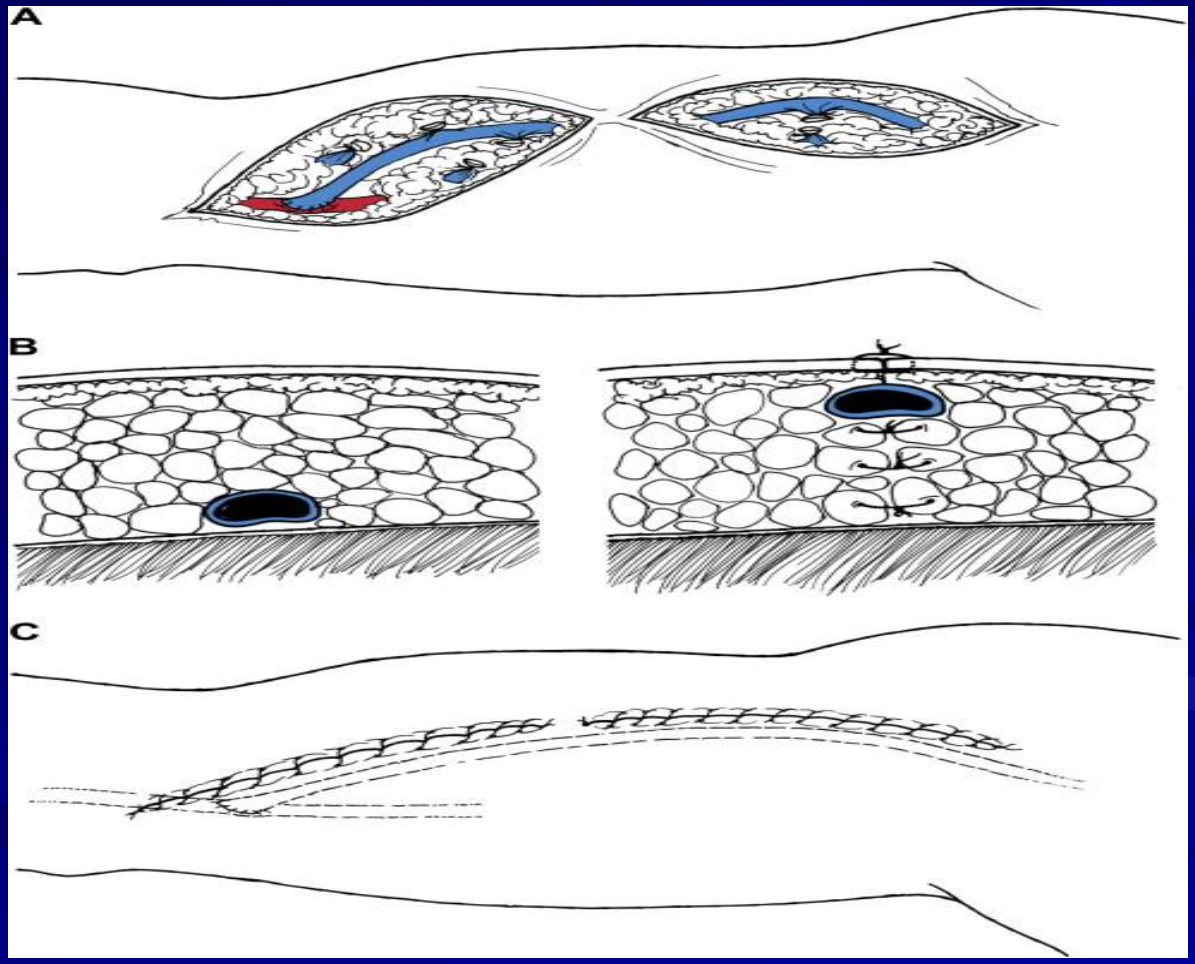
Secondary patency rates



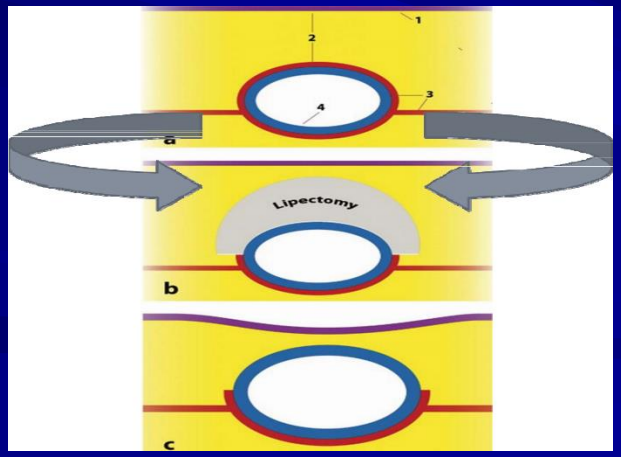
Strategies with proven benefit to make fistula vein more accessible i.e closer to the skin

- Vein transposition
- Removal of over lying fat

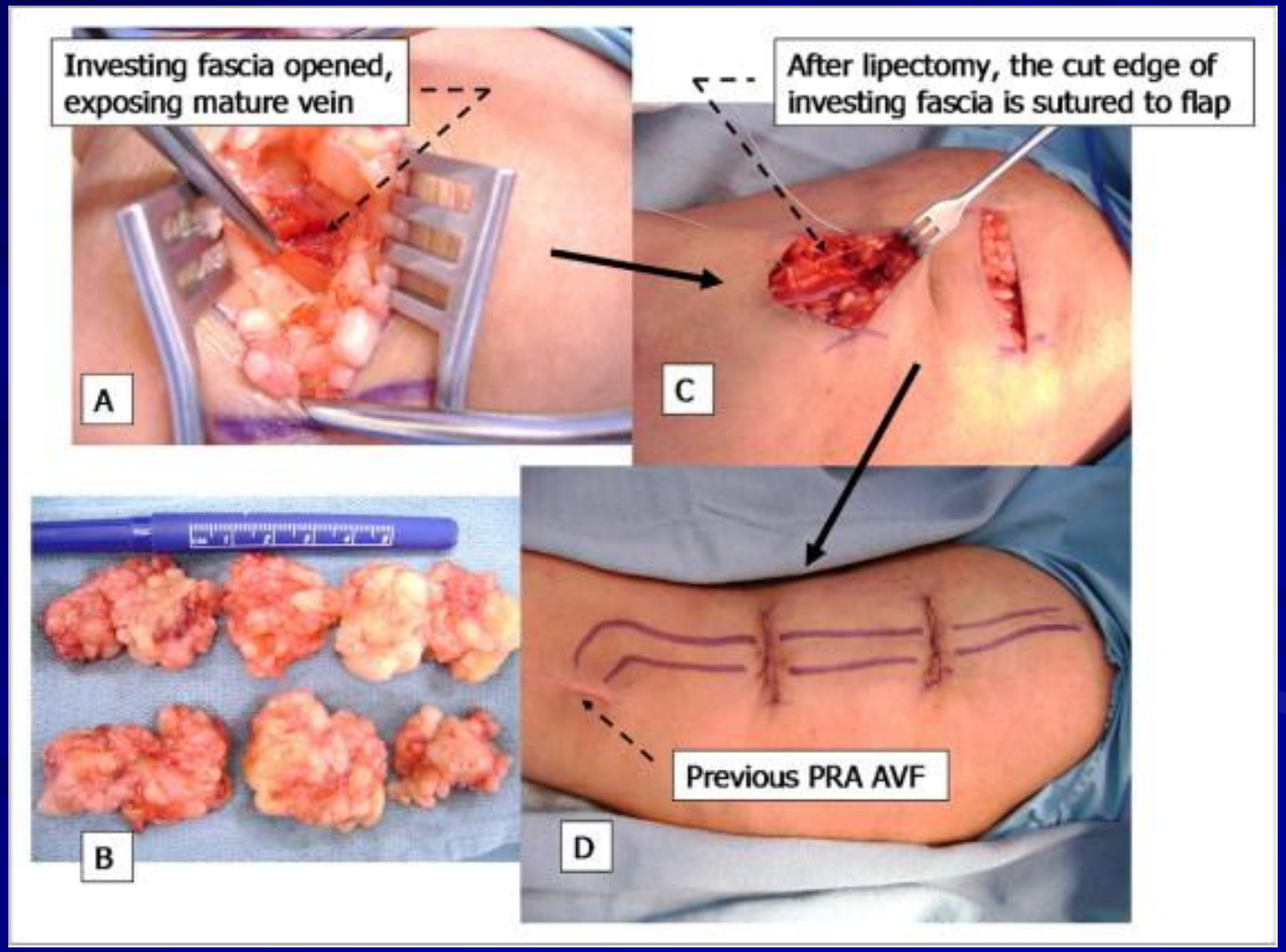
Vein transposition



Suction Lipectomy



Open lipectomy



Issues with renal transplantation in the obese

Surgical complications

Medical complications

Outcomes

Short term impact of obesity on renal transplantation

- Numerous studies have shown consistent associations of obesity with increased risks of short-term complications after kidney transplantation including:
- Wound complications
- Delayed graft function
- Acute rejection episodes
- Early graft loss
- Longer length of transplant hospitalization

- Meier-Kriesche HU, Arndorfer JA, Kaplan B. The impact of body mass index on renal transplant outcomes: a significant independent risk factor for graft failure and patient death. Transplantation. 2002;73:70–74.
- Morbidly obese recipients were significantly more likely to incur adverse graft events, including bleeding, DGF, prolonged hospitalization, early graft loss, acute rejection episodes
- Aalten J, Christiaans MH, de Fijter H, et al. The influence of obesity on short- and long-term graft and patient survival after renal transplantation. Transpl Int. 2006;19:901–907.
- Lynch RJ, Ranney DN, Shijie C, et al. Obesity, surgical site infection, and outcome following renal transplantation. Ann Surg. 2009;250:1014–1020.

Technical considerations

- High BMI impacts on access to waiting list
- Donor BMI cut off for living donation

- Central obesity makes surgical access more difficult – longer operating times, longer ischaemia times.
- Increased length of stay
- Greater risk of technical complications, wound seroma, wound infection/breakdown, incisional hernia
- Greater risk of respiratory problems

Impact of obesity on operating time and graft related complications

- BMI > 30 155 ± 59 mins
- BMI ≤ 30 119 ± 44 mins

- Increased risk of lymphocoele, renal artery stenosis, renal vein thrombosis.

- Singh D, Lawen J, Alkhudair W. Does pretransplant obesity affect the outcome in kidney transplant recipients? Transplant Proc. 2005;37:717–720.
- Behzadi AH, Kamali K, Zargar M, Abbasi MA, Piran P, Bastani B. Obesity and urologic complications after renal transplantation. Saudi J Kidney Dis Transpl. 2014;25:303–308

Impact of obesity on length of stay (Meta-analysis)

- BMI > 30

Range = 8.4 to 24.9 days

Median = 13.7 days

Mean = 14.9 days

- BMI ≤ 30

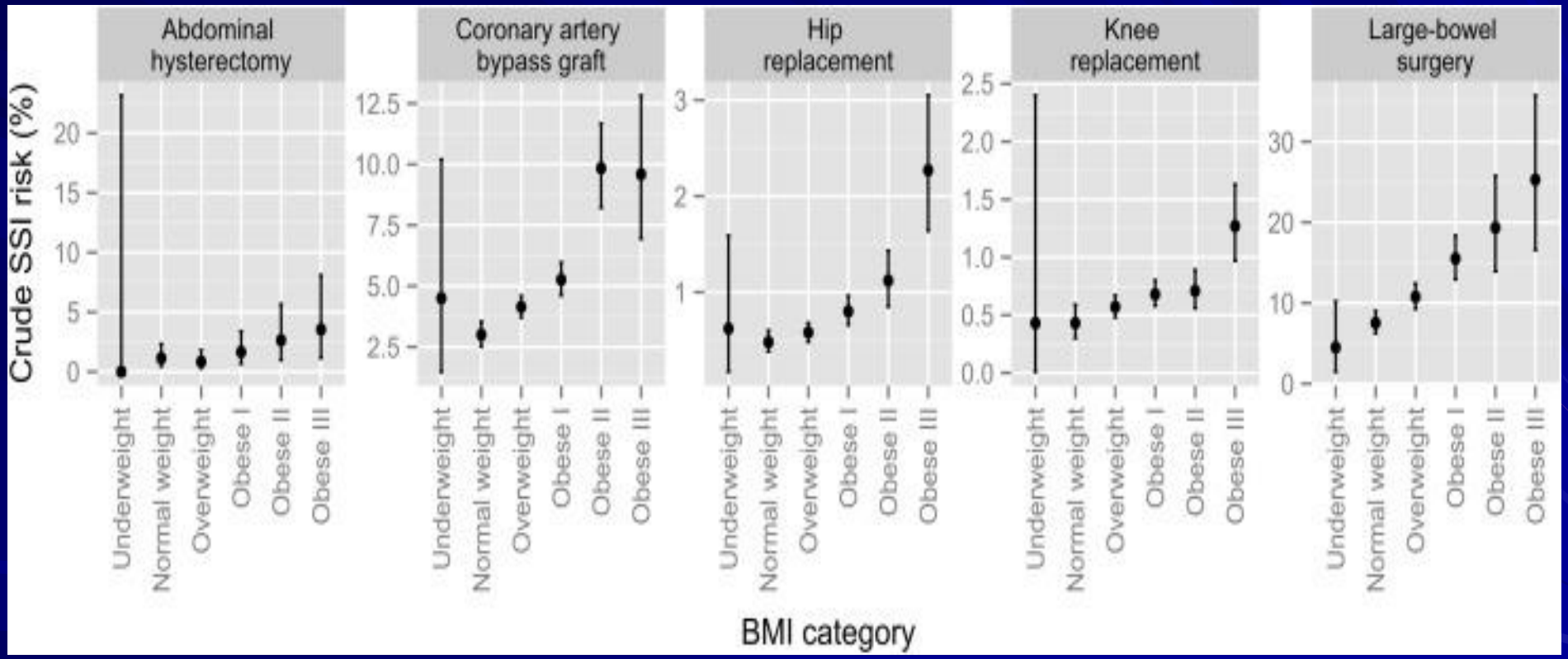
Range = 6.4 to 15.6 days

Median =9.5 days

Mean = 11.32 days

- Kidney transplantation in obese patients. Minh-Ha Tran, et al.
- World J Transplant. 2016 Mar 24; 6(1): 135–143.

Surgical site infection risk



Incisional hernia risk

Factors

- Greater risk of wound seroma/infection
- Higher incidence of diabetes
- Raised intra abdominal pressure
- Longer wound
- Longer operation time

Wound Complications

- Study of 2212 renal transplant recipients looking at incidence of wound infection, wound dehiscence, incisional hernia.
- BMI 30-34.9 = 17.5%
- BMI 35-39.9 = 29.0%,
- BMI 40-44.9 = 45.0%
- BMI>45 = 60%

- Risk increased 1.9-fold for each 5 points of BMI ($p<0.001$)
- Evidence for lower incidence of wound problems with robotic surgery

- **Obesity: A Major Risk Factor for Wound and Parietal Complications in Renal Transplantation.** Andrade, H. et al. Transplantation: July 15, 2014 - Volume 98 - Issue - p 522

Incisional Hernia

Repair can be technically challenging

Repair of midline hernias (the type that occur in 9% with robotic approach) is much easier

Medical issues

- Impact on Primary Graft Function
- Acute Rejection
- Risk of graft failure
- Impact on co-morbidity

Impact on Primary Graft Function

- 11,836 hemodialysis patients in the Scientific Registry of Transplant Recipients who underwent kidney transplantation.
- Mean BMI was 26.8 kg/m^2.

- Compared with patients with a pretransplant BMI of 22–24.9 kg/m^2,
- BMI 25–29.99 kg/m^2 – Odds Ratio = 1.30
- BMI 30–34.99 kg/m^2 – Odds Ratio = 1.42
- BMI >35 kg/m^2 - Odds Ratio = 2.18

- Conclusion: Pretransplant overweight or obesity is associated with an incrementally higher risk of DGF.

- Molnar MZ, Kovesdy CP, Mucsi I, et al. Higher recipient body mass index is associated with post-transplant delayed kidney graft function. Kidney Int. 2011;80:218–224.

Acute Rejection

- 1151 adult first renal graft recipients from a single institution
- Recipient BMI of 30 to 34.9 and ≥35 kg/m2 were associated with an increased risk of delayed graft function (odds ratio [95% confidence interval [CI], 1.92 [1.16–3.19] and 4.49 [2.24–9.00], respectively).
- BMI≥35 kg/m2 was associated with an increased risk of BPAR (hazard ratio [HR; 95% CI], 2.43 [1.48–3.99]), all-cause graft failure (HR [95% CI], 1.97 [1.09–3.56]), and death-censored graft failure (HR [95% CI], 2.43 [1.07–5.51]).

- Increased Recipient Body Mass Index Is Associated With Acute Rejection and Other Adverse Outcomes After Kidney Transplantation
- Curran, S et al. Transplantation: 2014; 97 : 1 - p 64–70

Acute Rejection – possible mechanisms (1)

- Obesity promotes a state of low-grade inflammation that exacerbates chronic inflammatory diseases, such as asthma and inflammatory bowel disease. In transplantation, the survival of organs transplanted into obese patients is reduced and acute rejection more frequent compared with allografts in lean recipients.
- Experimentally animals rendered obese through a high fat diet altered the composition and phenotype of splenic antigen-presenting cells leading to enhanced capacity to stimulate T cells.
- Cardiac allograft rejection in mice rendered obese through a high fat diet was modestly accelerated compared to aged-matched control animals fed a low-fat diet, correlating with enhanced alloreactive T cell function.

- High-Fat Diet–Induced Obesity Enhances Allograft Rejection
- Molinero, Luciana L. et al Transplantation: May 2016 - Volume 100 - Issue 5 - p 1015–1021

Acute Rejection – possible mechanisms (2)

- Altered pharmacokinetics associated with difficulties in dosing
- Sequestration of lipophilic drugs in adipose tissue
- Worsened ischemia-reperfusion injury due to increased warm ischemia time during the transplant procedure causing reduced adiponectin levels. Adiponectin has anti-inflammatory properties

Long term outcomes

Effect of degree of obesity on renal transplant outcome

	1yps	5yps	1ygs	5ygs
BMI 30-34.9	98.9	95.6	98.9	94.5
BMI>35	87.5	79.2	75	63
P value	0.07	0.06	<.0001	.0001

- Cacciola et al Transplant Proc. 2008 Dec;40(10):3408-12.

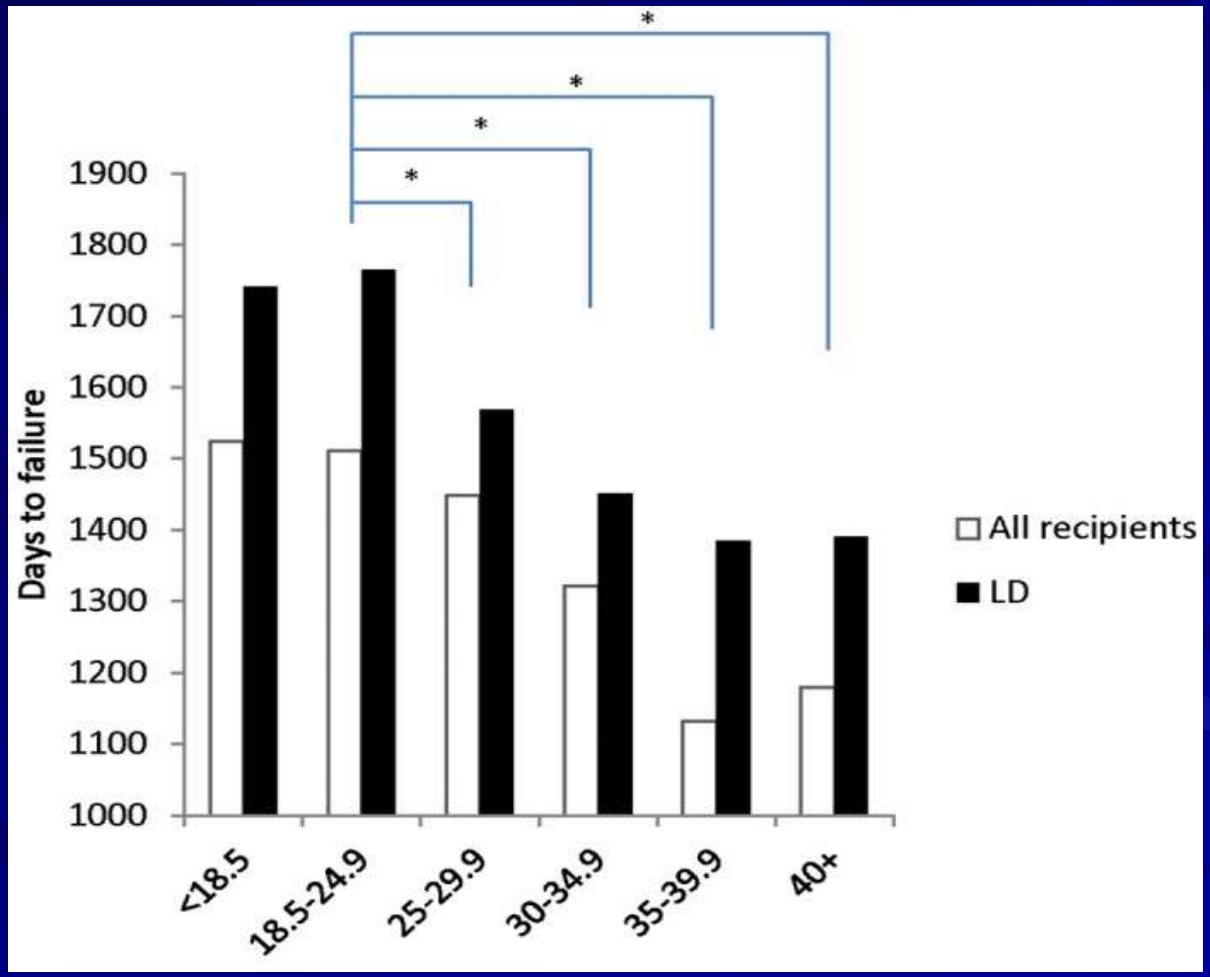
Risk of allograft failure

- Organ procurement and Transplantation Network Database
- 108654 recipients
- Taking BMI 18.5-25 as reference
- Hazard ratio for allograft failure
- 25-29.9 1.05 (P=0.01)
- 30-34.9 1.15 (P<0.001)
- 35-39.9 1.21 (p<0.001)
- >40 1.13 (p=0.002)

- Authors conclusion: In both unadjusted and adjusted models, increasing BMI was associated with increased risk of long-term allograft failure

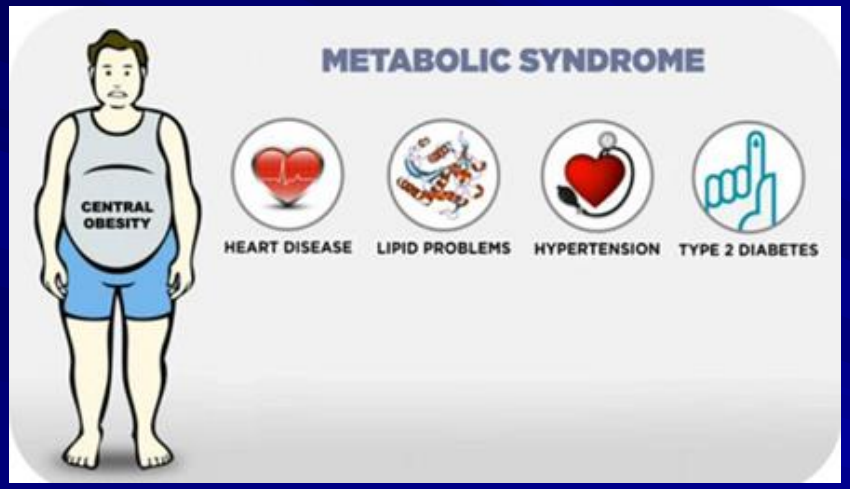
- The Impact of Obesity on Allograft Failure After Kidney Transplantation: A Competing Risks Analysis. Naik, Abhijit S. et al. Transplantation: 2016, 100; 9; 1963–1969

Mean Days to Renal Graft Failure versus Recipient BMI



Obesity related co-morbidity; Transplant related co-morbidity

- The obesity related CV risk factors are made worse by immunosuppression:



- Steroids – dyslipidaemia, hypertension, diabetes
- mTOR inhibitors – dyslipidaemia, diabetes
- CNIs - dyslipidaemia, hypertension, diabetes

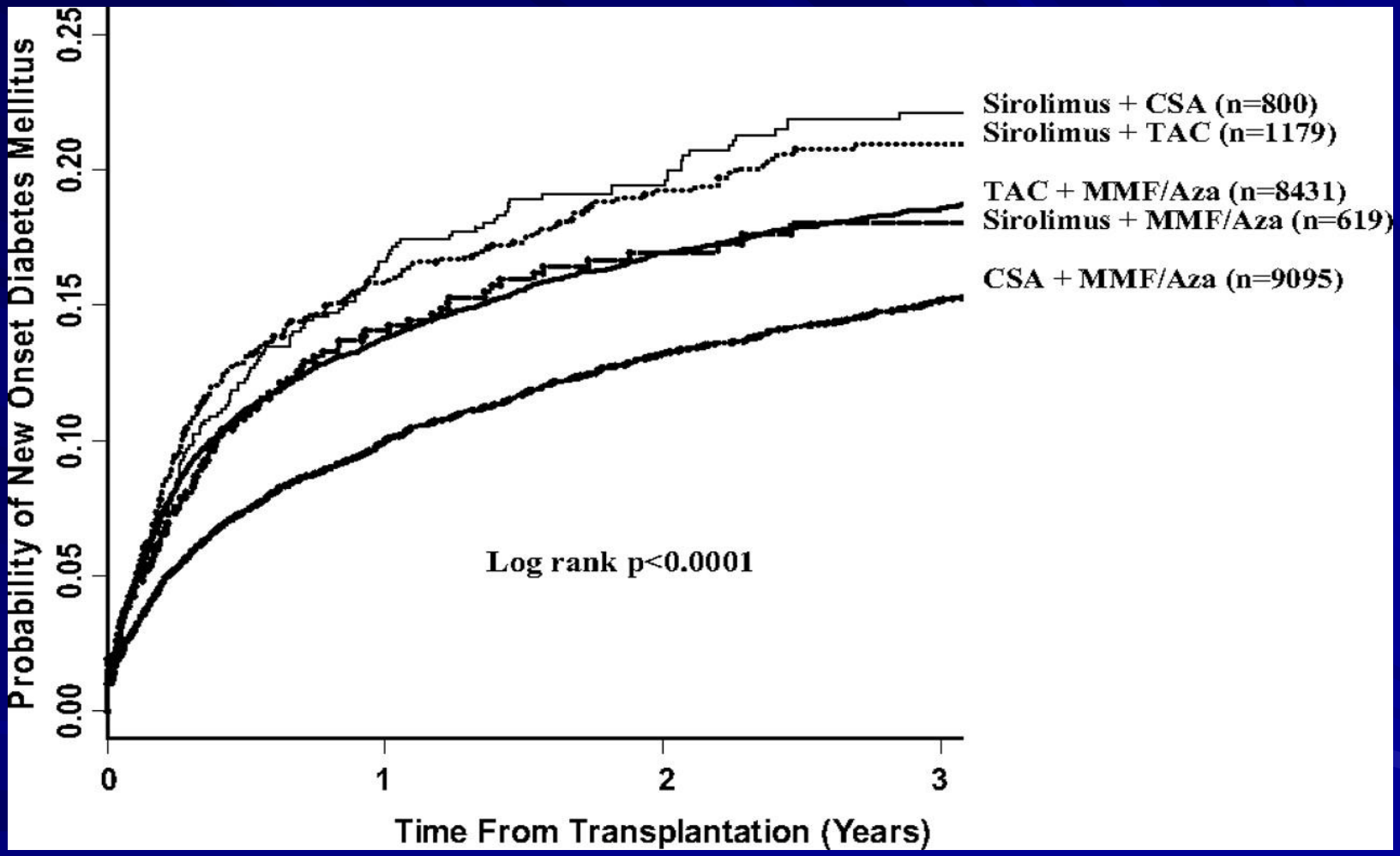
Risk of type 2 diabetes

- In males – increase waist circumference from <87.5cm to >101.6cm increases risk of type 2 diabetes 12 fold

- If BMI>25, risk increases 5 fold
- If BMI>35, risk increases 93 fold

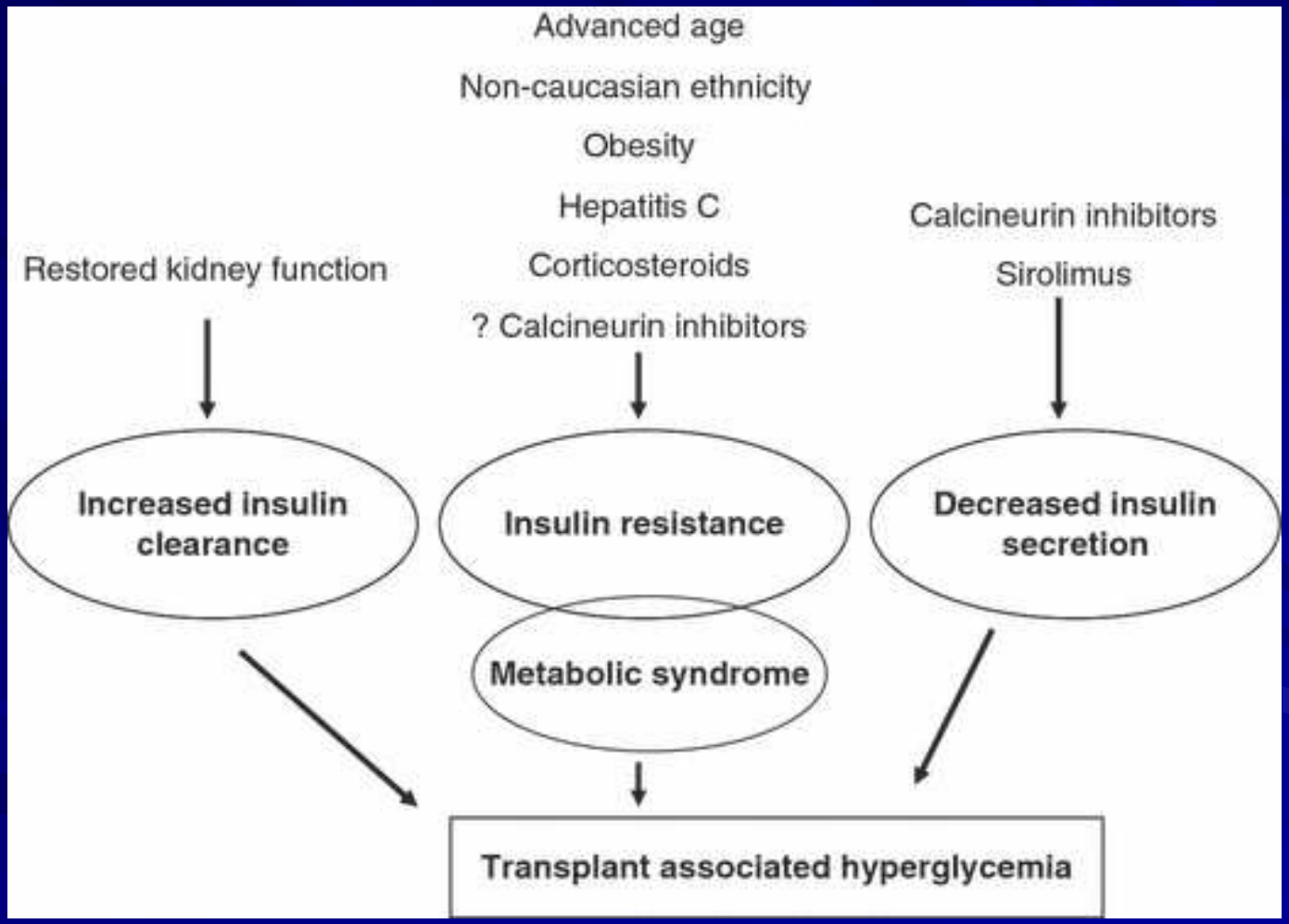
New-onset diabetes mellitus develops in approximately 20% of renal transplant recipients and is a known complication of immunosuppressive drugs.

Cumulative incidence of NOD within the first 3 yr posttransplantation by drug combination at hospital discharge from transplantation



Johnston O et al. JASN 2008;19:1411-1418

NODAT
(new onset diabetes after transplantation)



NODAT

- Obesity is an independent predictor of NODAT
- NODAT is a strong, independent predictor of renal graft failure and patient mortality

- BMI>30 RR of NODAT - 1.73 (1.53 for Tacrolimus use)
- NODAT mortality RR =1.87
- Graft failure RR= 1.63
- Death censored graft failure RR = 1.46

Cardiac risk of obesity

- Based on Framingham Heart Study
- Risk of death within study period (26 yrs) increases by:
  1% per pound overweight for 30-42 year olds
  2% per pound overweight for 50-62 year olds

BMI 25-30 equates to 3 years loss of life

BMI >30 equates to 7 years loss of life

BMI >40 equates to 15 years loss of life

BMI > 30 + smoking equates to 13 years loss of life

Impact of donor BMI

- 1132 deceased donor kidney transplants. Donors divided into four groups by BMI
- >30, 25-30, 20-25 and < 20 kg/m2.
- Kaplan-Meier and log-rank analysis were carried out for 5-year patient and graft survival.
- Five-year-graft survival of recipients receiving a graft from a donor with a BMI >30 kg/m^2, was 60,2% and significantly lower than in all other groups (78.0%, 80.4% and 85.9%, p=0.016).
- Patient survival in this cohort was similarly inferior with 74.9% after 5 years compared to 86.9%, 89.2% and 91.2% (p=0. 017)

- Weissenbacher, A et al, Transplantation: 2012 - 94 - 10S - p 270

Interventions

- Lifestyle – diet and exercise
- Pharmacological
- Surgical
  - Gastric bypass
  - Lap-band
  - Sleeve gastrectomy

Lifestyle changes

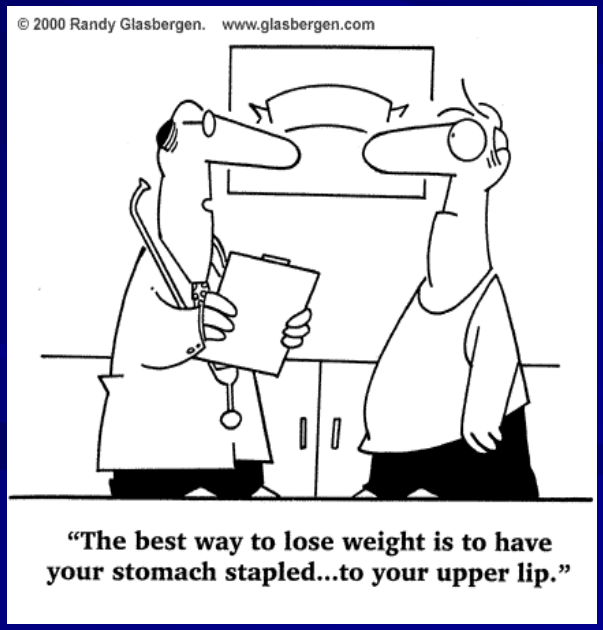
- Diet and exercise
- May be unsafe to diet if protein malnourished, despite high BMI.
- May be unable to exercise due to debility, uraemia
- Rarely useful pre-operatively but should be attempted post-operatively

Pharmacological: Orlistat

- Not absorbed – lumenal lipase inhibitor
- Prevents absorption of around 30% of ingested fat.
- Causes weight loss by malabsorption and behaviour modification as oral fat will induce bloating, steatorrhoea and faecal incontinence.
- Theoretical concern about lipophylic immunosuppressive drug absorption.

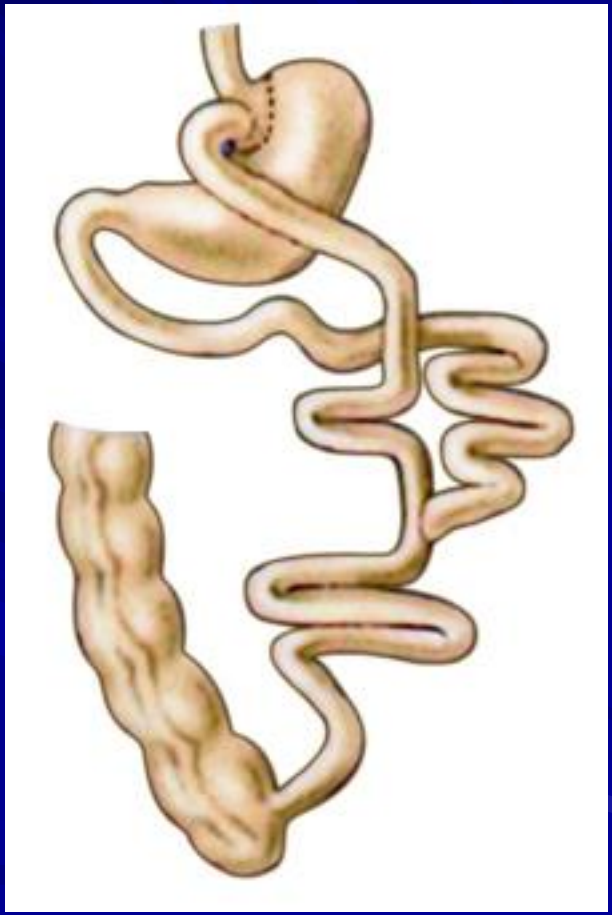
Bariatric surgery

- Gastric bypass
- Gastric band
- Sleeve gastrectomy



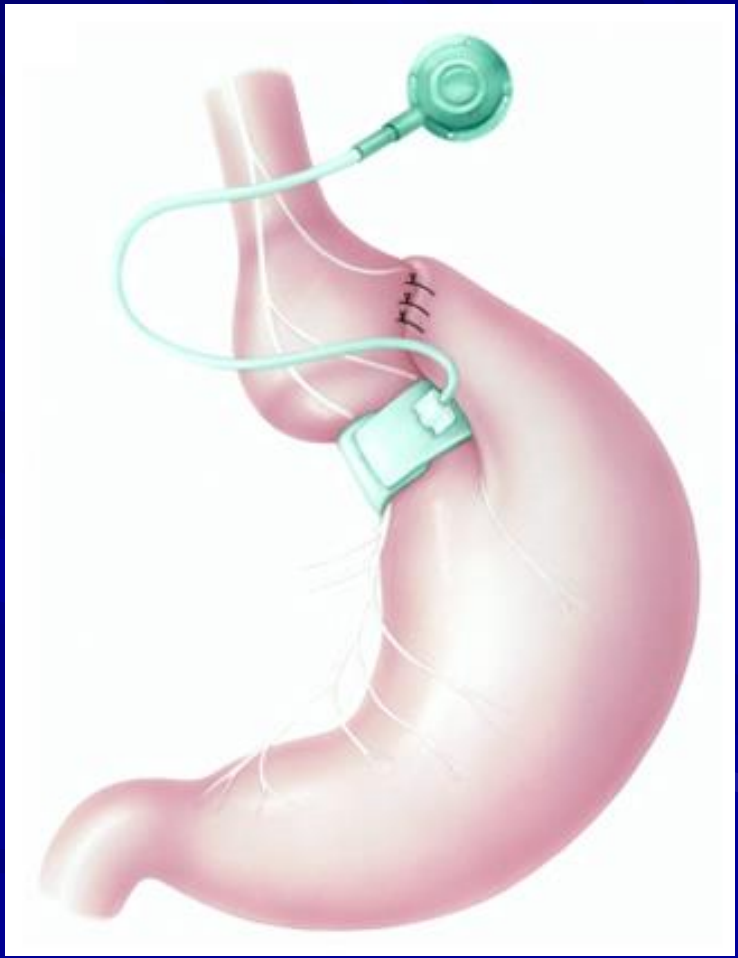
Roux-en-Y gastric bypass

- Gastric restriction
- Modest degree of malabsorption
- Hypoglycaemic dumping in response to refined carbohydrates



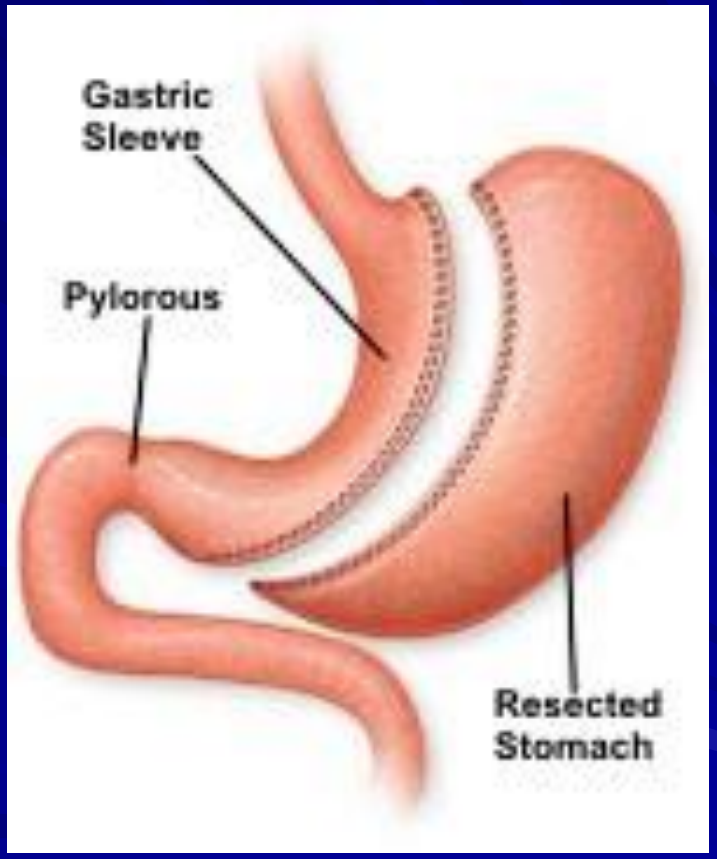
Laparoscopic Band

- Laparoscopically inserted balloon catheter to encircle upper stomach
- Subsequent inflation of balloon in steps to create a small gastric pouch with controlled but adjustable outlet
- Works by gastric restriction alone.



Sleeve gastrectomy

- Resection of 80% of stomach
- Risk of post-op staple line leakage
- Purely restrictive; absorption normal
- No adjustment or maintenance needed



Bariatric surgery

? Prior to transplantation surgery
? At the time of transplantation
? After transplantation
? At all

<u>Issues</u>

Available skills (time of transplant)
Implanted foreign body (lap band)
Absorption of drugs (vomiting, malabsorption gastric bypass)
Sleeve probably the most appropriate

Liver Transplant + bariatric surgery

- Liver Transplant + sleeve gastrectomy
- **44 pts with BMI>35, dieted to BMI<35**
  - **Group 1 37 pts underwent LT**
  - **Group 2 7 pts underwent LT + SG**

- **Group 1** **3 deaths + 3 graft losses**
  21/34 regained to >35.
  12/34 NODM. 7/34 NAFLD

- **Group 2** **0 deaths + 0 graft losses.**
  0 regained weight. (Av BMI 29).
  0/7 NODM. 0/7 NAFLD

- Heimbach et al AJT 2013; 13: 363-8

Impact of weight loss surgery on cardiovascular risk factors

- Diabetes
- Hypertension
- Global cardiac risk

Impact of bariatric surgery on diabetes

- Bariatric surgery alters energy balance
- Meta-analysis 135,000 patients; 621 studies
- 103 studies report remission of type 2 diabetes of 78.1%
- Only one randomised study investigating bariatric surgery versus no surgery for type 2 diabetes. 73% versus 13% after 2 years.

- Dixon et al. Diabetic Medicine 2011

Impact of bariatric surgery on hypertension

95 patients with established hypertension undergoing bariatric surgery

72% female, Mean BMI 47

Mean excess body weight loss = 66% at 12 months

Mean systolic BP fell from 140+/-17 to 120+/-18

Mean diastolic BP fell from 80+/-11 to 71+/-8

46% complete resolution (related to shorter duration of disease)

19% improved

- Hinojosa. J Gastroint Surg 2009; 13: 793-7

Impact on cardiac risk factors (1)

- 52 studies with full data set,

16,967 patients. 78% female, mean age 42. All procedures.

- Baseline prevalence
  - Hypertension 49%
  - Diabetes 28%
  - Dyslipidaemia 46%
- Mean Follow-up 34 months
- Excess weight loss 52% (16-87%)

Outcome Mean BP fall from 139/87 to 124/77

40% relative risk reduction as determined by Framingham

- Am J Cardiol 2011

Impact on cardiac risk factors (2)

- Framingham and PROCAM (Prospective cardiovascular Munster Heart Study) risk scores applied to calculate 10 year CV risk in 197 bariatric surgery patients and 163 controls

Framingham 10 year risk score
7.0 to 3.5% in bariatric patients
7.1 to 6.5% in controls

PROCAM 10 year risk score
4.1 to 2.0% in bariatric patients
4.4 to 3.8% in controls

- i.e longitudinal cardiac risk halved by bariatric surgery

- Batsis et al. Am J Cardiol 2008; 102: 930-7.

Impact on cardiac risk factors (3)

- Retrospective study of bariatric patients using Framingham risk equation

- Predicted baseline 10 year cardiovascular risk was 6.7 +/- 5.5%
- At 12 months risk had fallen to 3.2 +/- 3.1%
- Relative risk reduction of 52%
- Systolic BP 143+/-20 to 123 +/-18
- Diastolic BP 81+/-10 to 71 +/-11
- Total cholesterol 202 to 165
- LDL-C 118 to 97
- HDL-C 45 to 51

- Kligman et al. Surgery 2008; 143: 533-8

Impact of weight loss pre-transplant

- Data collected from USRDS (United States Renal Data System) on 162,284 adult (18-70) ESRD patients with BMI data recorded of which 124,713 were transplanted.
- Survival advantage of obesity in dialysis patients
- Decline in BMI on the waiting list was not protective for post-transplant mortality or graft loss.
- Substantial weight loss pretransplantation was associated with rapid weight gain post-transplantation.
- The highest risk for death was patients with pathologically low BMI (13-18.5 kg/m(2), adjusted hazard ratio = 1.47, $p < 0.01$).
- While observed declines in BMI may be volitional or markers of disease processes, there is no evidence that candidates have improved transplant outcomes attributable to weight loss which is rarely sustained

- Schold et al. Am J Transplant. 2007 Mar;7(3):550-9)

Summary (1)

- Large retrospective studies consistently show that renal transplant recipients with high BMI have diminished graft and patient survival following transplantation
- Obesity in transplant recipients is associated with increases in: complication rates, costs, length of stay, delayed graft function , acute rejection, graft loss, NODAT, death following the procedure.

- Despite the relatively superior prognosis for obese patients as compared to non-obese patients on dialysis and a relatively inferior prognosis following transplantation, kidney transplantation still significantly increases life expectancy in this portion of the ESRD population.

Summary (2)

- Obesity is made worse by transplantation.
- Transplantation is made worse by obesity
- Worsening problem in society which may contribute to the increasing need for renal transplantation.
- The common CV risk factors (diabetes, hypertension, dyslipidaemia) are made worse by obesity and by immunosuppression
- Role for bariatric surgery post-transplant not defined

Predictions are risky, particularly when made about the future"

Senator Dan Quayle, Former U.S. Vice President

Thank you