Obésité
Quelles conséquences sur la fonction rénale?

Dr Vincent Bourquin - service de néphrologie - http://nephrohug.com
“Let me have men about me that are fat, Sleek-headed men, and such as sleep o’nights: Yond Cassius has a lean and hungry look; He thinks too much: such men are dangerous.”

Source: Julius Caesar, Act 1, Scene 2 William Shakespeare (1564-1616)
“In recent years, there has been an alarming rise in the prevalence of chronic kidney disease that has paralleled the increase in the prevalence of obesity....”

“Increasing evidence suggests that obesity is a potentially important contributor to the development of CKD.”

NON, NON !
PAS D’ÉRYTHRO POUR VOUS, MON AMI !
Evolution surpoids en Suisse

1992

BMI 25-30: 24.9
BMI > 30: 5.4

2007

BMI 25-30: 29.2
BMI > 30: 8.1

Source: http://bag.admin.ch
Obésité en Suisse

- Population sans excès pondéral: 70.8%
- Excès pondéral (IMC > 25): 29.2%
- Adiposité (IMC > 30): 8.1%

Source: [http:bag.admin.ch](http:bag.admin.ch)
“...it appears that the peak level in the adult overweight and obese segment of the Swiss population may be reached in the near future, i.e. the next few years, or – under best circumstances – may have been passed already.”

Source: http://bag.admin.ch
“Bien que la prévalence des maladies rénales en relation avec l’obésité ne soit pas clairement définie, plusieurs études récentes ont montré une corrélation significative entre l’IMC d’une part, et la survenue d’une protéinurie ou d’une insuffisance rénale d’autre part”

“Four patients with massive obesity and the nephrotic syndrome were studied. In each case the proteinuria decreased during dietary weight loss. A mesangial glomerulopathy was present in two patients.”

“In the following years, several case reports describing glomerulosclerosis in very obese patients have been published, but this entity was considered as rare and rather bizarre.”

Source: Prof G. Wolf Contribution to Nephrology 2006
“The degree of albuminuria showed piecewise log-linear relationship with body mass index (P = 0.0001)”

5670 people older than 40 years

“We found that BMI was associated with an increased risk of the development of end stage of renal disease in men in the general population in Okinawa.”

100’753 screenees, during follow-up 404 screenees developed ESRD

“Overweight (BMI > 25) at age 20 was associated with a significant three-fold excess risk for chronic renal failure.”

926 case patients and 998 control subjects

“After mean follow-up of 18.5 years, 244 participants (9.4%) developed kidney disease. Body mass index with odds ratio 1.23 (95% CI 1.08-1.41).”

2’585 participants with baseline and follow-up examination

“After an average 14-year follow-up, 1’377 participants (12.4%) had a GFR less than 60 mL/min/1.73 m². Higher baseline BMI was associated consistently with increased risk for CKD (OR 1.45)”

11’104 initially healthy men provided a blood sample after 14 years

“The study found that those with morbid obesity had more than double the risk of CKD (OR 2.3) compared to normal weight individuals, independent of age, sex, race, smoking and physical activity.”

9'082 adults with an average follow-up of 13.2 years.

Source: Stengel et coll. Epidemiology 2003
“In HDFP participants without CKD at baseline, the incidence of CKD at year 5 was 28% in the ideal-body-mass-index group, 31% in the overweight group (OR 1.21) and 34% in the obese group (OR 1.40).”

5’897 hypertensive adults

**Source:** Kramer et coll. Am J Kidney Dis 2005
Obesity-related glomerulopathy

“ORG was defined morphologically as **focal segmental glomerulosclerosis** and **glomerulomegaly** or **glomerulomegaly alone.**”

6’818 native renal biopsies

**Source:** Kambham et coll. Kidney Int 2001
Obesity-related glomerulopathy

glomérulosclérose segmentaire et focale

Obesity-related glomerulopathy
discrète sclérose mésangiale focale et lésions “diabétoïdes”

Obesity-related glomerulopathy

épaississement focal de la membrane basale

Obesity-related glomerulopathy

glomérulomégalie

<table>
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<tr>
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<th>Glomérulopathie liée à l’obésité</th>
<th>HSF idiopathique</th>
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<tbody>
<tr>
<td>Protéinurie d’ordre néphrotique</td>
<td>48 %</td>
<td>66 %</td>
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<tr>
<td>Syndrome néphrotique</td>
<td>5.6 %</td>
<td>54 %</td>
</tr>
<tr>
<td>Oedèmes</td>
<td>35 %</td>
<td>68 %</td>
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<tr>
<td>Albumine sérique g/l</td>
<td>39</td>
<td>29</td>
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<tr>
<td>Cholestérol sérique mg/dl</td>
<td>229</td>
<td>335</td>
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<tr>
<td>Sclérose focale</td>
<td>10 %</td>
<td>39 %</td>
</tr>
<tr>
<td>Glomérulomégalie</td>
<td>100 %</td>
<td>10 %</td>
</tr>
<tr>
<td>Fusion podocytaire</td>
<td>40 %</td>
<td>75 %</td>
</tr>
</tbody>
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**ORG is distinct from idiopathic FSGS**

**Source:** Kambham et coll. Kidney Int 2001
“Obesity has not only been suggested to cause renal disease but also to accelerate its deterioration.”

Source: Prof G. Wolf Contribution to Nephrology 2006
“In a cohort of 162 incident patients with biopsy-proven immunoglobulin A (IgA) nephropathy, the presence of an elevated BMI at RBI was significantly associated with the severity of pathological renal lesions.”

“BMI showed a very strong association with outcome after renal transplantation. BMI was also associated with an increased risk for delayed graft function...”

51'927 primary, adult renal transplant registered in the USRDS

Source: Meier-Kriesche et coll. Transplantation 2002
“Higher body-mass index and elevated blood pressure independently increase the long-term risk of renal-cell cancer in men.”

363'992 Swedish men

“The positive association between obesity and kidney disease is a relationship that is both complex and not yet fully understood.”

The interrelationship between adiposity and maladaptive changes in the heart and kidney

**Dysfunctional adipose tissue**
- Macrophage infiltration
- Low-grade inflammation
- Increased IL-1, IL-6, TNF-α
- Elevated leptin

↑ Aldosterone
↑ Angiotensin II
NADP oxydase
ROS production
Hyperuricemia
Sympathetic activation
RAAS activation
Oxidative stress
Inflammation

Hyperfiltration-related maladaptive mechanisms

Endothelial dysfunction

Hyperfiltration

Microalbuminuria

• Na-retention
• Glomerular sclerosis
• Tubulointerstitial fibrosis
• Proteinuria
• Decreased GFR

Glomerular filtration rate (GFR) and renal plasma flow (RPF) were determined by measuring inulin and PAH clearance. In the obese group, GFR exceeded the control value by 61% and RPF by 32%. Consequently, filtration fraction (FF) was increased.

\[
\frac{\text{GFR}}{\text{RPF}} = (\text{FF})
\]

Forces physiques

compression rénale extrinsèque et intrinsèque

“Abnormal kidney function, caused by increased renal tubular reabsorption, initiates volume expansion and increased blood pressure during excess weight gain, and the hypertension and metabolic abnormalities associated with obesity, in turn, contribute to chronic renal disease.”

Source: Hall JE Hypertension 2003
Obésité augmente réabsorption tubulaire du sodium...

**Source:** Hall JE Hypertension 2003
“Les cytokines sécrétées par le tissu adipeux (adipokines), induisent une hyperactivité sympathique par le biais de la leptine, et un état inflammatoire de bas grade qui contribue au développement de lésions de sclérose glomérulaire, d’autant qu’il existe une résistance à l’adiponectine.”

Source: Prof M. Laville Nephro Ther 2011
**Substances vasoactives et profibrosantes**

**Angiotensine**: Rôle important dans le développement et la progression de la néphropathie. Effet sur l’hypertension intraglomérulaire et la perméabilité sélective de la membrane basale glomérulaire.

**Insuline**: Stimule la synthèse facteurs de croissance, tels que IGF-1 et 2, promoteurs probable d’hypertrophie glomérulaire. Vasodilatation artériole afférente, augmentation hypertension intraglomérulaire.

**Rénine**: Augmentation, ainsi que l’aldostérone.

**Leptine**: Action pro-inflammatoires et profibrotique. Rôle dans la survenue de l’hypertension chez sujet obèse. Stimulation du système sympathique.

**Transforming growth factor-β (TGF-β)**: Augmentation

**Tumor necrosis factor-α (TNF-α)**: Augmentation

**Plasminogen activator inhibitor-1 (PAI-1)**: Augmentation

**Interleukine-6**: Augmentation

**Résistine**: Augmentation. Insulinrésistance, inflammation.

**Adiponectine**: Diminution sous l’influence de la fétuine avec insulinorésistance, inflammation, dysfonction endothéliale, stimulation SRAA et finalement HTA. Régulation perméabilité glomérulaire.

**Source**: Mathieu et coll. Rev Med Suisse 2006
vasoconstriction artériole afférente
Effet sur artériole

*insulin-induced vasodilatation*

**Source:** Juncos et coll. J Clin Invest 1993
“The obese Zucker (ZDF-fa/fa) rat, with hyperinsulinaemia and hyperlipidemia develops progressive renal failure associated with an accentuated podocyte injury and glomerulosclerosis.”

Source: Hoshi and coll. Lab Invest 2002
“Normal rats infused with leptin developed proteinuria and focal glomerulosclerosis. Interactions between the activated RAAS and leptin appear to play an important role in oxidative stress within endothelial cells and contribute to the pathogenesis of atherosclerosis.”

Source: Correia et coll. Curr Opin Nephrol Hypertension 2004
“Adiponectin (ADPN), whose levels are reduced in obesity and insulin resistance, was strongly implicated in the pathogenesis of kidney injury in obesity.”

“ADPN-deficient mice exhibited effacement and fusion of podocyte foot process as well as increased albuminuria. Administration of ADPN led to attenuation in podocyte damage together with a reduction in albuminuria.”

HOUH! VOUS ÊTES BIEN TROP GROSSE, MADAME!

JE SAI, DOCTEUR... MAIS C'EST À CAUSE DE L'OBÉSITÉ...
“Le traitement de choix des néphropathies associées à l’obésité est la réduction du poids corporel.”

“There was significant correlation between body weight loss and decrease in proteinuria.”

17 obese patients with proteinuria > 1g/day

Source: Praga et coll. Nephron 1995
“In a small Japanese case series, 25 patients with BMI > 25 who were hypertensive and microalbuminuric with preserved renal function were placed in a low-caloric diet (25 kcal/kg) with significant improvement in microalbuminuria and blood pressure over 1-year follow-up in the 12 patients who achieved a weight reduction of at least 5%.”

Source: Kuiper J.J. Nephron 1996
“En présence d’une hyperfiltration, d’une hyperactivité du SRAA, a fortiori d’une microalbuminurie ou d’une protéinurie, l’administration d’inhibiteur de l’enzyme de conversion est logique. Cependant, leur effet sur la protéinurie peut n’être que transitoire en l’absence de perte de poids stable, ce qui limite leur action néphroprotectrice.”

“17-year-old girl with morbid obesity (BMI 56.8) and ORG presenting with nephrotic range proteinuria, who failed to improve following treatment with diet, exercise and ACEI/ARB therapy. **Laparoscopic gastric bypass surgery** was performed, and within 2 weeks following the surgery, the patient had lost 5.7 kg body weight and showed a remarkable decrease in protein excretion to one tenth of pre-surgery levels.”

**Source:** Fowler et coll. Pediatr Nephrol 2009
“Obese patients with renal failure can safely undergo bariatric surgery and that bariatric surgery may have a role in treating chronic kidney disease in select morbidly obese patients.”

“BMI may not be ideal due to its inability to reliably distinguish visceral obesity from subcutaneous fat nor is able to differentiate a high body weight due to muscle mass from fat (or oedema).”

“More studies are required to identify a more reliable measure of kidney function in the obese, but until then the use of non-corrected GFR in combination with calibrated serum creatinine has been recommended in these individuals.”

“Reverse epidemiology is a term for the medical hypothesis which holds that the influence of obesity and high body weight indexes may be protective and associated with greater survival in obese patient in haemodialysis.”

Source: R Stolic Med Hypotheses 2010
“Higher BMI (up to 45) and higher serum creatinine concentration were incrementally and independently associated with greater survival, even after extensive multivariate adjustment for available surrogates of nutritional status and inflammation.”

5-year cohort of 121’762 patients receiving HD 3x/week

merci de votre attention