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TITRE

Metabolic abnormalities differentially affect albuminuria and glomerular filtration rate in the general population

Jury

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RESUME

Introduction :

L'obésité et le diabète augmentent le risque de maladie rénale chronique. Néanmoins, le fait que d'autres anomalies métaboliques, comme le syndrome métabolique ou le risque de stéatose hépatique non alcoolique (NASH), puissent être associées à des anomalies de fonction rénale, et qu'elles puisent affecter différemment l'albuminurie et le débit de filtration glomérulaire est mal décrit. De même, l'association entre prédiabète et anomalies rénales avant l'apparition du diabète n'est pas décrite dans la littérature.

Patients et Méthodes :

Etude transversale en population générale**.**

Résultats :

En tout**,** 118.314 patients de 40 ans et plus ont été inclus. Une altération de la fonction rénale (albuminurie pathologique (≥30mg/g) et/ou la diminution du débit de filtration glomérulaire estimé (eDGF<60mL/min/1,73m²) a été observée chez 5.3% des patients. L'association entre l'indice de masse corporelle (IMC) et l'albuminurie pathologique décrivait une courbe en J, alors que l'association de l'IMC avec la diminution du eDFG était continue. Comparés aux patients de poids normal, ceux en sous-poids (<18.5kg/m²) avaient un sur-risque d'albuminurie pathologique (OR 2.12 [1.55-2.83]). Il existait une relation continue entre le nombre de composants du syndrome métabolique et le risque d'albuminurie pathologique ou de diminution du eDFG. La présence d'un index de NASH élevé était un facteur de risque d'albuminurie pathologique et de diminution du eDFG. Enfin, un haut risque de développer un diabète était associé à un sur-risque d'albuminurie pathologique, et de diminution du eDFG. Le risque d'albuminurie pathologique était plus marqué que celui de baisse du eDFG, et ce quelle que soit l'anomalie métabolique considérée.

Conclusion :

La relation entre IMC et albuminurie anormale décrit une courbe en J. Les anomalies métaboliques, telles que le syndrome métabolique et la NASH, sont associées à l'albuminurie pathologique et dans une moindre mesure à la diminution du eDFG, suggérant une association préférentielle avec la dysfonction endothéliale. Le risque rénal pourrait précéder le risque de diabète.

Metabolic disturbances differentially affect albuminuria and glomerular filtration rate in the general population.

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Abstract

Introduction: Obesity and diabetes mellitus increase the risk of chronic renal disease. However, it is presently unknown whether all metabolic abnormalities, such as metabolic syndrome or nonalcoholic steatohepatitis are associated with impaired renal function, and whether they affect similarly albuminuria and glomerular filtration rate. Whether prediabetic state is associated with abnormal albuminuria before the occurence of diabetes is also unknown.

Methods: Large cross-sectional study in the general population.

Results: Overall, 118,314 subjects aged 40 years and over were included in the present study. Impaired renal function (abnormal albuminuria (≥30 mg/g) and/or low estimated glomerular filtration rate (eGFR<60 ml/min/1.73m²)) was observed in 5.3% of subjects. The association between body mass index (BMI) and abnormal albuminuria was a J-curve whereas the association with low eGFR was continuous. As compared to subjects with normal BMI, underweight subjects had a greater risk of abnormal albuminuria (OR: 2.12 [1.55-2.83]).

There was also a continuous relationship between the number of components of the metabolic syndrome and the risk of abnormal albuminuria or of low eGFR. However, the risk of abnormal albuminuria was much greater than the risk of low eGFR, for all metabolic disturbances. The presence of a high fatty liver index was a risk factor for abnormal albuminuria and for low eGFR. Finally, a high risk of developing diabetes was associated with elevated albuminuria, and to a lesser extent with low eGFR.

Conclusion: There is a J-curve relationship between BMI and abnormal albuminuria. Metabolic disturbances, such as metabolic syndrome and nonalcoholic steato-hepatitis, are associated with abnormal albuminuria, and to a lesser extent with low eGFR, suggesting a preferential association with endothelial dysfunction. Renal risk may precede the risk of diabetes mellitus.

Mots-clefs :

Anomalies métaboliques

Syndrome métabolique

Stéatose hépatique non alcoolique

Maladie rénale

Débit de filtration glomérulaire

Albuminurie

Sous-poids

Risque de diabète

Key words :

Metabolic abnormalities

Metabolic syndrome

Non alcoholic steatohepatitis

Kidney disease

Glomerular filtration rate

Albuminuria

Underweight

Diabetes risk

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En présence des Maîtres de cette Faculté,
de mes chers condisciples
et selon la tradition d'Hippocrate,
je promets et je jure d'être fidèle aux lois de l'honneur
et de la probité dans l'exercice de la Médecine.
Je donnerai mes soins gratuits à l'indigent,
et n'exigerai jamais un salaire au-dessus de mon travail.
Admis dans l'intérieur des maisons, mes yeux
ne verront pas ce qui s'y passe, ma langue taira
les secrets qui me seront confiés et mon état ne servira pas
à corrompre les mœurs ni à favoriser le crime.
Respectueux et reconnaissant envers mes Maîtres,
je rendrai à leurs enfants
l'instruction que j'ai reçue de leurs pères.
Que les hommes m'accordent leur estime
si je suis fidèle à mes promesses.
Que je sois couvert d'opprobre
et méprisé de mes confrères
si j'y manque.

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Table des matières :

Introduction

The prevalence of obesity is increasing all over the world, and has more than doubled worldwide between 1980 and 2008 [1]. In 2010, the International Obesity Task Force estimated this number to be 475 to 600 million adults, and 40 to 50 million school aged children [2]**.** However, it is now acknowledged that the consequences of obesity on cardiovascular diseases are mainly observed in subjects with metabolic syndrome. Therefore, it has appeared as more relevant to study the cardiovascular consequences of metabolic abnormalities than those of obesity only. Metabolic syndrome initially included the association of high blood pressure, large waist circumference, low HDL-cholesterol, high triglycerides and impaired fasting glucose. Later on, it appeared that other metabolic changes such as nonalcoholic steatohepatitis (NASH) [3], hyperuricemia [4], or iron metabolism disorders [5], could be associated with metabolic syndrome. Finally, using a few of these parameters, scores to predict the risk of diabetes mellitus were developed [6,7].

At the same time, the epidemic of chronic kidney disease (CKD) was observed in all countries [8]. In the USA for example, the prevalence of CKD has increased from 10.0% to 13.1% between the 1988-1994 and the 1999-2004 NHANES studies [9]. The main causes remain diabetes and hypertension-related renal diseases, both conditions highly influenced by obesity and metabolic impairment [10–12]. Interestingly, it was found that obesity and the metabolic syndrome could be associated with elevated albuminuria [13] (a marker of both renal disease and endothelial dysfunction), even in non-diabetic patients [14] ; however, the relationship between obesity and glomerular filtration rate appeared more complicated since it was associated with glomerular hyperfiltration in some reports but reduced renal function in others. In contrast, it was shown that underweighted subjects may have endothelial dysfunction, which may also -especially in children- increase urinary albumin excretion, but it is unsure whether underweight constitutes a renal risk [15–17]. Altogether, these data suggested

that weight may differentially affect albuminuria and glomerular filtration rate. Data regarding the effect of the other parameters indicating metabolic impairment (such as components of the metabolic syndrome, fatty liver index, diabetes risk scores) on albuminuria and estimated glomerular filtration rate are scarce. It is presently unknown whether the renal (i.e. effects on albuminuria and estimated glomerular filtration rate (eGFR)) consequences of obesity are the same as those of the other components of the metabolic syndrome, fatty liver index or diabetes risk scores.

In this present large cross sectional study, we carefully evaluated the association between metabolic disorders, albuminuria and eGFR in the general population.

Subjects and Methods

Selection of the population

Subjects included in the present cross sectional study attended medical examination in one of the 11 Institut inter Régional pour la Santé (IRSA, France) centers from january 2006 to december 2010 [18,19]. IRSA is a non lucrative association aiming to develop preventive medicine and health promotion, which offers subjects affiliated to the national insurance health system free medical examination every five years.

The study was restricted to subjects aged 40 to 79 years old. Subjects with missing urinary albumin excretion (UAE), serum creatinine, systolic (SBP) or diastolic (DBP) blood pressure values, fasting glucose value, having experienced fever or practicated intensive physical activity the day before, pregnant women, and women having their period were excluded. Subjects with personal history of renal disease were also excluded.

Parameters

Every subject filled a self-administered sociomedical questionnaire including questions about socioprofessional category, familial and personal medical history. Fasting blood samples and urinary samples were collected in each subject. Medications were checked by a physician. Weight and height were measured in light clothes. Blood Pressure (BP) was measured in lying subjects after at least 5 minutes of rest, with an automatic Omron® device. Physical activity was defined according to three questions on duration and regularity of physical activity at home, at work, and sport practice.

Definitions

All blood samples were collected after overnight fasting for about 12 hours. Several biochemical parameters were assessed on the C8000 Architect Abbott analyzer. Fasting glucose was measured by Hexokinase method. UAE was measured by immunoturbidimetry. HDL cholesterol was evaluated by direct enzymatic method. Urine albumine was measured by direct kinetic Jaffe's method.

LDL cholesterol was calculated according to Friedewald equation[20]. Diabetes mellitus was assessed by the use of at least one glucose lowering medication or a fasting glucose level over 7.0 mmol/L. Abnormal albuminuria was defined as an urine albumine to creatinine ratio ≥ 30 mg/g. eGFR was calculated according to the abbreviated Modification of Diet in Renal Disease (MDRD) equation[21]. Low eGFR was defined as an eGFR <60mL/min/1.73m² [22].Underweight was defined as body mass index (BMI) <18.5 kg/m². Obesity was defined as BMI ≥ 30 kg/m². Reference weight was defined as BMI between 18.5 and 24.9 kg/m² [23]. Waist circumference was defined as the smallest circumference between the lower ribs and the iliac crests. Not recommended physical activity was assessed if subjects didn't report at least one intensive activity out of the three types of physical activity and didn't report important sport practice associated with important physical activity at home or at work. The

Fatty Liver Index (FLI) was calculated according to the Bedogni formula in subjects drinking less than 30g of alcohol per day in men and 20 g per day in women. This index varies from 0 to 100, a score ≥ 60 indicating a risk of hepatic steatosis[24]. Hypertension was defined as a SBP ≥140 mmHg or DBP ≥90 mmHg. Smoking was defined as current smoking or smoking weaned for less than a year. A diabetes risk score was calculated according to the DESIR score, in nondiabetic subjects, as previously reported. A clinical score of 5 indicates a 9-year diabetes risk of >30% [7]. The metabolic syndrome was defined according to NCEP ATP III definition (i.e. the presence of at least 3 of the following parameter: HDL cholesterol <1.04 mmol/L for men or 1.29 mmol/L for women, fasting glucose ≥ 6.1 mmol/L or glucose lowering medication, triglycerides ≥ 1.69 mmol/L or lipid lowering medication, blood pressure ≥ 130/85 mmHg or antihypertensive medication, waist circumference ≥ 102 cm for men or 88 cm for women [25,26]).

Statistical analyses

Results are given in means (standard deviation) or percentages, except for triglycerides, fasting plasma glucose and cholesterol, given in median (quantile 1 – quantile 3) and log-transformed for the analysis, because of skewed distribution. The comparison between groups was made with covariance analysis for continuous data and logistic regression for discrete data with adjustment on age and gender. We studied the associations between the various components of metabolic risk (such as BMI, number of components of the metabolic syndrome, fatty liver index, the estimated risk of diabetes) and abnormal albuminuria (a marker of both endothelial and renal dysfunction) and low eGFR, respectively by logistic regression with adjustments on age and gender. Analysis were made with R version 2.13.1 (Free Software Foundation, Boston, MA, USA). Significance was defined as a p value < 0.05.

Results

Characteristics of the population

Overall, 128,766 patients were aged 40 to 79 years old. After application of the exclusion criteria, 118,314 patients were included in the present study; 61,481 (52.0%) were men. Mean age was 53.9 ± 8.9 in men, and 53.7 ± 8.6 in women. The prevalence of diabetes was 5.5 %, the prevalence of hypertension was 44.7%. The prevalence of metabolic syndrome was 17.0%, and 16.1% of the subjects were active smokers.

As shown in Table 1, abnormal albuminuria (≥30 mg/g) with normal eGFR was found in 2,613 subjects whereas low eGFR (<60 ml/min/1.73m²) was observed in 3,686 subjects.

Subjects with abnormal albuminuria and normal eGFR were more frequently of male gender (71.3% vs 52.1%), with hypertension (74.7% vs 43.4%), obesity (32.1 vs 14.6%), metabolic syndrome (41.4 vs 16.1%), fatty liver index ≥ 60 (50.7 vs 22.9%), low physical activity (83.3 vs 76.6%), and a calculated diabetes risk score > 30% at 9 years (9.5 vs 3.4%) compared to subjects with normal renal function. The prevalence of diabetes mellitus and the proportion of subjects using lipid-lowering therapy were also greater (Table 1).

Subjects with low eGFR had more frequently hypertension (63.3% vs 43.4%), treated hypertension (38.9% vs 16.4%), obesity (21.3 vs 14.6%), metabolic syndrome (29.9 vs 16.1%), fatty liver index ≥ 60 (33.1 vs 22.9%), low physical activity (80.0 vs 76.6%), a calculated diabetes risk score > 30% at 9 years (5.6 vs 3.4%) compared to subjects with normal renal function ; however, the proportion of male gender was lower (33.2 vs 52.1%) (Table 1).

BMI and risks of abnormal albuminuria and low eGFR

As depicted in Fig.1, there was a J-curve relationship between BMI and the prevalence of abnormal albuminuria (≥30 mg/g), after adjustment on age and gender. As compared to

subjects with normal BMI (18.5 to 24.9 kg/m^2), underweight subjects had a greater risk of abnormal albuminuria (OR: 2.12 [1.55-2.83], P=0.0003). Interestingly, underweight subjects had significantly less hypertension (22.2 vs 32.2%, P<0.00001), LDL cholesterol levels (3.33 (0.83) vs 3.61 (0.84) mmol/L, P<0.00001), waist-to-hip ratio (0.79 (0.07) vs 0.85 (0.08) , P<0.00001) and higher HDL levels (1,78 (0.41) vs 1,60 mmol/L (0.37), P<0.00001) vs subjects with reference weight (BMI: 18.5 to 24.9 kg/m^2); however, they were more frequently smokers (31.3% vs 19.8%, P<0.00001) as compared to subjects with reference weight. Among subjects with BMI ≥ 25 kg/m^2, there was a continuous relationship between BMI and abnormal albuminuria (vs normal BMI defined as BMI 18.5-24.9 kg/m^2): OR: 1.36 [1.24-1.50], 2.66 [2.39-2.97], 4.14 [3.52-4.86] and 7.37 [5.84-9.15] in subjects with BMI 25 to 29.9, 30 to 34.9, 35 to 39.9 and ≥40 kg/m^2, respectively.

In contrast, the relationship between BMI and low eGFR was continuous among all BMI classes (including underweight): as compared to normal BMI, OR were 0.79 [0.57-1.06], 1.30 [1.20-1.40], 1.52 [1.37-1.68], 1.57 [1.31-1.87] and 2.07 [1.57-2.68] in subjects with BMI <18.5, 25 to 29.9, 30 to 34.9, 35 to 39.9 and ≥40 kg/m^2, respectively (Table 2).

Metabolic syndrome and risks of abnormal albuminuria and low eGFR

As shown in Fig.2, there was a continuous relationship between the number of components of the metabolic syndrome (after adjustment on age and sex) and the risk of abnormal albuminuria and the risk of low eGFR,. However, the risk of abnormal albuminuria was far greater than the risk of low eGFR, for each number of components of the metabolic syndrome.

In effect, as compared to subjects with no component of the metabolic syndrome, the risk of abnormal albuminuria measured by the OR was 2.05 [1.74-2.44], 3.29 [2.78-3.92], 5.32 [4.47-6.36], 9.89 [8.24-11.91] and 15.14 [12.01-19.06] in subjects with 1, 2, 3, 4 or 5 components

of the metabolic syndrome, respectively. The risk of low eGFR was 1.13 [1.01-1.26], 1.54 [1.37-1.73], 1.89 [1.66-2.14], 2.16 [1.86-2.51] and 2.56 [2.01-3.22], respectively in subjects with 1, 2, 3, 4 or 5 components of the metabolic syndrome (Table 3).

Fatty Liver Index categories and risks of abnormal albuminuria and low eGFR

Fatty liver index could be estimated in only 46,092 subjects. As shown in Fig.3, the association between the risk of fatty liver and the risk of renal abnormalities was continuous. Subjects with a FLI ≥ 60 had the greater risk of abnormal albuminuria (OR 3.56 [3.03-4.20]) and low eGFR (OR 1.88 [1.59-2.23]) as compared to those with fatty liver index<30; subjects with a fatty liver index between 30 and 60 had intermediate risk (OR were 1.48 [1.22-1.79] and 1.47 [1.24-1.75] for the risk of abnormal albuminuria and low eGFR, respectively (Fig.3, Table 4)).

Risk of diabetes and risks of abnormal albuminuria and low eGFR in nondiabetic subjects

For this analysis, relevant data were available in 88,223 subjects. There was a continuous association between the calculated 9-year risk of diabetes and the risk of prevalent renal abnormalities; however the risk was especially significant for abnormal albuminuria and to a lesser extent for low eGFR (Fig.4).

As compared to patients with a null score of incident diabetes, the patients with a score of 3, 4, or 5, had a significant risk of abnormal albuminuria (OR: 2.25 [1.64-3.18], 3.95 [2.88-5.57] and 6.11 [4.33-8.83], respectively) and of low eGFR (OR: 1.43 [1.13-1.83], 1.72 [1.36-2.21] and 1.60 [1.20-2.15], respectively). (Fig.4, Table 5).

Discussion

In the present study, we found that around 5% of healthy subjects from the general population had low eGFR or abnormal albuminuria. In addition, metabolic syndrome, high fatty liver index and estimated risk of diabetes mellitus were associated with abnormal albuminuria and low eGFR; interestingly, there was a J-curve relationship between BMI and the risk of abnormal albuminuria whereas the relationship between BMI and the risk of low eGFR was continuous across all BMI classes; there was a continuous relationship between renal dysfunction (either abnormal albuminuria or low eGFR) and the number of components of the metabolic syndrome, high fatty liver index and the calculated 9-year risk of diabetes.

In our large, cross sectionnal study in general population, 5.3% of subjects over 40 years old had occult kidney disease. To our knowledge, this is the first estimation of the prevalence of occult kidney disease in a French population. In 2012, the MONA LISA study [27] estimated the prevalence of decreased eGFR at 8.2% in a general population, by studying a representative sample (4,727 subjects) in another French population, but did not take in account albuminuria. The prevalence of decreased eGFR was greater in the Mona Lisa study than in our cohort, despite similar population age, proportion of subjects with hypertension or diabetes. This may be explained by the fact that in our study, a personal history of renal disease was an exclusion criterion, not in the Mona Lisa study. In 2007, the prevalence of low eGFR was 13.1% in the NHANES 1999-2004 study [9]; however, the NHANES population included up to 15% non caucasian subjects, whereas our population was almost exclusively Caucasian[28,29]. However, this lower rate of occult kidney disease is in accordance with the lower incidence and prevalence of terminal chronic kidney disease in France than in the USA (In 2010, its prevalence in France was 1,060 par million population [30], versus 1,752 in the USA [31]).

We observed a J-curve relationship between BMI and abnormal albuminuria due to the fact that underweight subjects had a surprisingly greater risk of abnormal albuminuria. Underweight subjects were more frequently smokers than subjects with normal weight, but the association between albuminuria and low-body weight persisted after adjustment on smoking habits (data not shown). Since there was no relationship with low eGFR, it is possible that abnormal albuminuria in underweight subjects represents a marker of greater cardiovascular risk, and may not be a renal risk per se. Other explanations can be proposed: low current weight may be explained by low birth weight, another risk factor for elevated albuminuria. In healthy elderly people (>55years), lower weight is correlated with increased C-reactive protein [15], suggesting low grade inflammation. Unfortunately, C-Reactive protein was not recorded in our population. Anorexic subjects are known to be at higher cardiovascular risk, linked with a prooxidative state and with endothelial dysfunction [32,33]. Whether they have also abnormal albuminuria is unknown. To the best of our knowledge, our study is the first one to show a greater risk of abnormal albuminuria in apparently healthy very lean subjects; this could be due to endothelial dysfunction rather than renal risk. However, this hypothesis needs to be confirmed by other studies.

There was a continuous relationship between renal dysfunction (either abnormal albuminuria or low eGFR) and the number of components of the metabolic syndrome. Metabolic syndrome is a cluster of metabolic abnormalities, such as abdominal adiposity, hyperglycemia, dyslipidemia, and hypertension. Various definitions exist. In the current study, we used NCEP ATP III definition, as it is a more powerful predictor of cardiovascular disease, and as this definition is used in most of the recent studies [25]. Metabolic syndrome is associated with decreased eGFR [34], even in nondiabetic subjects [35], and is associated with proteinuria, mostly in diabetic subjects. Recently, it was found that albuminuria predicted the development of chronic kidney disease, cardiovascular disease and diabetes mellitus in

subjects with metabolic syndrome [36]. In 2003, Pinto-Siesma et al showed that a central body fat distribution was associated with decreased eGFR, not only in obese but also in lean subjects [37]. As expected, in our study, not only metabolic syndrome was associated with chronic kidney disease, but the relation between the number of components of metabolic syndrome and the risk of abnormal albuminuria or low eGFR was continuous. These findings are in accordance with other results. In 2012, Cheng et al showed that metabolic syndrome was associated with incident chronic kidney disease; in 2005, Kurella et al indicated that metabolic syndrome was associated with the risk of decreased eGFR, and that the relation between number of components of metabolic syndrome and decreased eGFR was continuous. In 2004, Chen et al [38], in an adult U.S. Population, showed that subjects with metabolic syndrome had a greater risk of albuminuria or low GFR.

In the present study, there was a continuous relationship between renal dysfunction (either abnormal albuminuria or low eGFR) and higher high fatty liver indexes. NASH is a common cause of chronic liver disease, and its prevalence increases with obesity and diabetes. It is strongly linked to the clusters of metabolic syndrome [39]. In 2006, Bedogni et al developed a clinico-biological score (based on BMI, waist circumference, fasting triglycerides, and gamma-glutamyl transferase to predict the risk of NASH on the general population (a score <30 ruling out, and a score >60 ruling in, echographic hepatic steatosis [24]). It is known that the elevation of gamma-glutamyl transferase and the presence of hepatic steatosis is associated with chronic kidney disease in diabetics subjects but also in the general population [40–42]. In our study, we observed that the risk of NASH was associated with renal risk in the French population. Thus, people at risk for NASH should also be screened for chronic kidney disease.

Finally, we found that there was a continuous relationship between renal dysfunction (either abnormal albuminuria or low GFR) and the calculated 10-year risk of diabetes. The practical

consequences of such a finding are important: subjects with greater risk for diabetes mellitus should be considered at greater risk of chronic kidney disease. Moreover, since kidney dysfunction may be present before development of diabetes mellitus, such a result indicates that renal dysfunction is not necessarily the consequence of diabetes mellitus, but that both conditions can be caused by metabolic changes. This result may also explain, at least in part, that glomerular filtration rate can fall rapidly early during the course of diabetes mellitus as observed in some recent reports [43,44]. In effect, in the "classical" natural history of diabetes mellitus, it is stated that renal function decline should occur after the development of proteinuria i.e. after a long duration of the disease, not early in the course of the disease: our observation indicate that the pathophysiology of renal function decline is more complex, and that renal function can be low even before the development of diabetes mellitus.

In this state of mind, two observations in our study suggest that the mechanisms leading to abnormal albuminuria and those leading to low eGFR could be different. First, each metabolic abnormality studied was far more strongly associated to low abnormal albuminuria than to low eGFR. Second, as described upper, lean subjects had a greater risk of albuminuria, whereas their risk of low eGFR was similar to the one of normal weight subjects. We suggest that albuminuria could be the reflect of systemic endothelial dysfunction, whereas low eGFR could be the reflect of local hemodynamic abnormality, such as capillary rarefaction [45]. Further prospective studies are needed to explore this hypothesis.

Admittedly, our study has some limitations: First, our population is composed of apparently healthy people with no history of renal disease. Thus, subjects with known renal disease are not represented in this population. However, our estimation of occult renal disease is probably not overestimated. Second, this study is retrospective, and we lack some information, such as biological markers of endothelial dysfunction. Nevertheless, it allowed us to work on a very

large population, and gives reliable data on the French population general health state. It is to our knowledge the largest study on the prevalence of kidney dysfunction in a French - or European - population.

Conclusion

Occult kidney disease is frequent in the French general population over 40. Metabolic dysfunction (metabolic syndrome, obesity, steatohepatitis, or diabetes risk) is correlated with renal risk. Underweight subjects are at risk for abnormal albuminuria, but is it unclear whether abnormal albuminuria represents here a marker of renal or cardiovascular risk. Finally, all subjects at risk for diabetes mellitus should be also considered at risk for renal dysfunction.

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Conflicts of Interests: none

Table 1. Characteristics of the population, expressed as mean (standard deviation) or percentage

	Normal Renal Function	Normal eGFR and abnormal UAE	Abnormal eGFR	p [4]
N	112,015	2,613	3,686	
Age (years)	53.5 (8.6)	56.7 (9.5)	60.8 (9.2)	<0.00001
Men (%)	52.1	71.3	33.2	<0.00001
Diabetes (%)	5.0	20.8	8.5	<0.00001
Treated hypertension (%)	16.4	33.3	38.9	<0.00001
Lipid-lowering medication (%)	12.5	22.4	27.4	<0.00001
BMI (kg/m²)	25.7 (4.4)	28.1 (5.6)	26.8 (4.8)	<0.00001
BMI ≥ 30 kg/m² (%)	14.6	32.1	21.3	<0.00001
DBP (mmHg)	134 (17)	148 (21)	139 (19)	<0.00001
SBP (mmHg)	80 (10)	87 (12)	81 (10)	<0.00001
Waist circumference (cm)	88.2 (12.7)	96.8 (14.4)	89.8 (13.6)	<0.00001
Total cholesterol (mmol/L) [1]	5.66 (5.04 – 6.31)	5.66 (4.94 – 6.41)	5.72 (5.04 – 6.41)	0.0007
LDL-cholesterol (mmol/L)	3.65 (0.86)	3.58 (0.99)	3.66 (0.90)	<0.00001
Triglycerides (mmol/L) [1]	1.05 (0.79 – 1.46)	1.35 (0.96 – 1.95)	1.14 (0.84 – 1.57)	<0.00001
HDL-cholesterol (mmol/L)	1.49 (0.36)	1.39 (0.41)	1.48 (0.38)	<0.00001
Fasting plasma glucose (mmol/L) [1]	5.11 (4.77 – 5.49)	5.44 (5.00 – 6.22)	5.11 (4.77-5.55)	<0.00001
serum uric acid (mg/L)	45.27 (12.83)	52.15 (14.52)	50.42 (14.96)	<0.00001
Metabolic syndrome NCEP ATP III (%)	16.1	41.4	29.9	<0.00001
DESIR score [2]	2.4 (1.2)	3.1 (1.2)	2.8 (1.2)	<0.00001
Fatty liver index [3]	35.6 (28.1)	56.1 (30.7)	44.9 (29.2)	<0.00001
Not recommended physical activity (%)	76.6	83.3	80.0	0.00004

1. Median (quantile 1 – quantile 3).
2. Diabetics subjects excluded [7]
3. Subjects with excessive alcohol consumption excluded [24]
4. covariance analysis for continous data or logistic regression for discrete data with adjustments on age and gender.
eGFR: estimated glomerular filtration rate UAE: urinary albumin excretion BMI: body mass index SBP: systolic blood pressure DBP: diastolic blood pressure

Table 2: Relation between renal risk and body mass index classes. Age and gender adjusted odds ratios and 95% confidence interval.

	BMI (kg/m²)					
	[18.5 – 25[(ref)	<18.5	[25-30[	[30-35[	[35-40[	> 40
Abnormal UAE	1	2.12 (1.55-2.83)	1.36 (1.24-1.50)	2.66 (2.39-2.97)	4.14 (3.52-4.86)	7.35 (5.84-9.15)
Low eGFR	1	0.79 (0.57-1.06)	1.30 (1.20-1.40)	1.52 (1.37-1.68)	1.57 (1.31-1.87)	2.07 (1.57-2.68)

UAE : urinary albumin excretion. eGFR: estimated glomerular filtration rate

Table 3: Relation between renal risk and number of components of the NCEP ATP III metabolic syndrome. Age and gender adjusted odds ratios and 95% confidence interval.

	Number of components of the metabolic syndrome NCEP ATP III definition					
	0 (ref)	1	2	3	4	5
Abnormal UAE	1	2.05 (1.74-2.44)	3.29 (2.78-3.92)	5.32 (4.47-6.36)	9.89 (8.24-11.91)	15.14 (12.01-19.06)
Low eGFR	1	1.13 (1.01-1.26)	1.54 (1.37-1.73)	1.89 (1.66-2.14)	2.16 (1.86-2.51)	2.56 (2.01-3.22)

UAE : urinary albumin excretion. eGFR: estimated glomerular filtration rate

Table 4: Relation between renal risk and steatosis risk. Age and gender adjusted odds ratios and 95% confidence interval.

	Steatosis risk		
	<30 (ref)	[30-60[	≥ 60
Abnormal UAE	1	1.48 (1.22-1.79)	3.56 (3.03-4.20)
Low eGFR	1	1.47 (1.24-1.75)	1.88 (1.59-2.23)

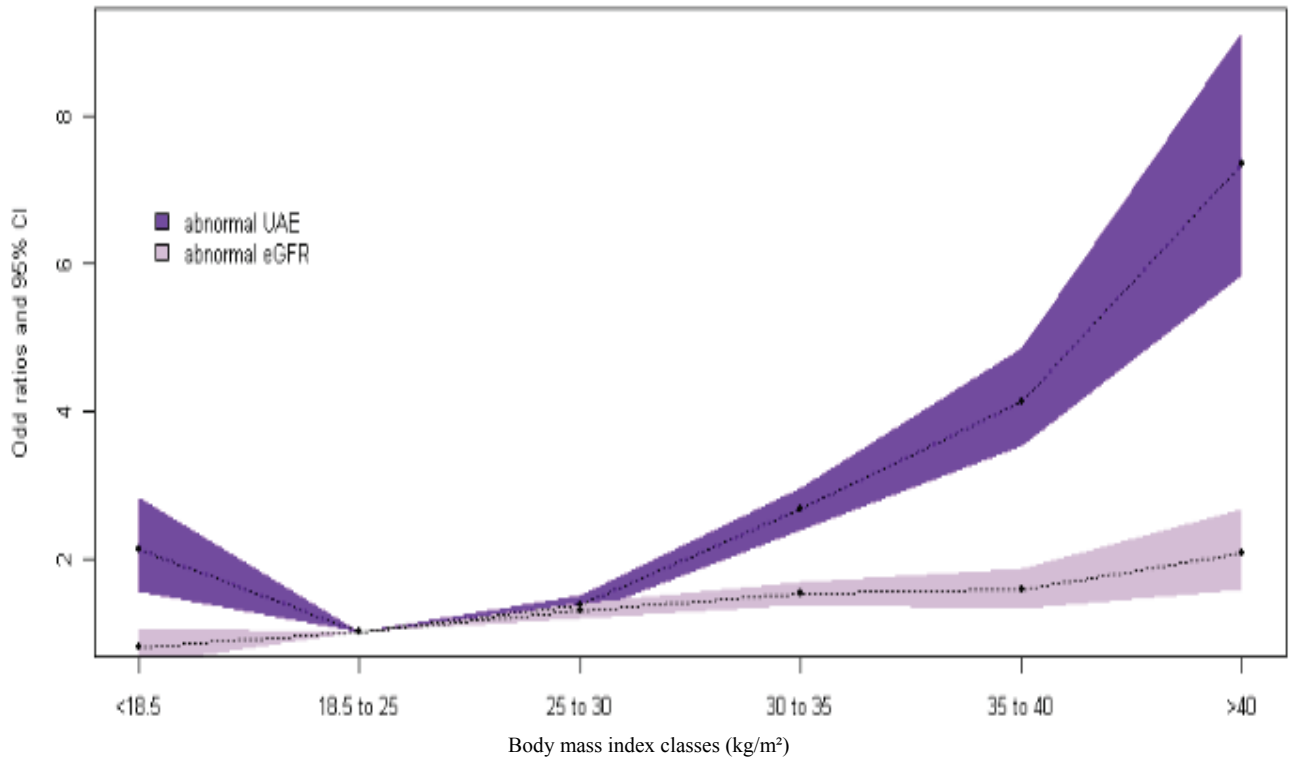
UAE : urinary albumin excretion. eGFR: estimated glomerular filtration rate

Table 5: Relation between renal risk and 9-year risk of incident diabetes (DESIR score). Age and gender adjusted odds ratios and 95% confidence interval.

	DESIR score					
	0 (ref)	1	2	3	4	5
Abnormal UAE	1	0.97 (0.69-1.41)	1.31 (0.95-1.86)	2.25 (1.64-3.18)	3.95 (2.88-5.57)	6.11 (4.33-8.83)
Low eGFR	1	1.00 (0.78-1.29)	1.13 (0.89-1.46)	1.43 (1.13-1.83)	1.72 (1.36-2.21)	1.60 (1.20-2.15)

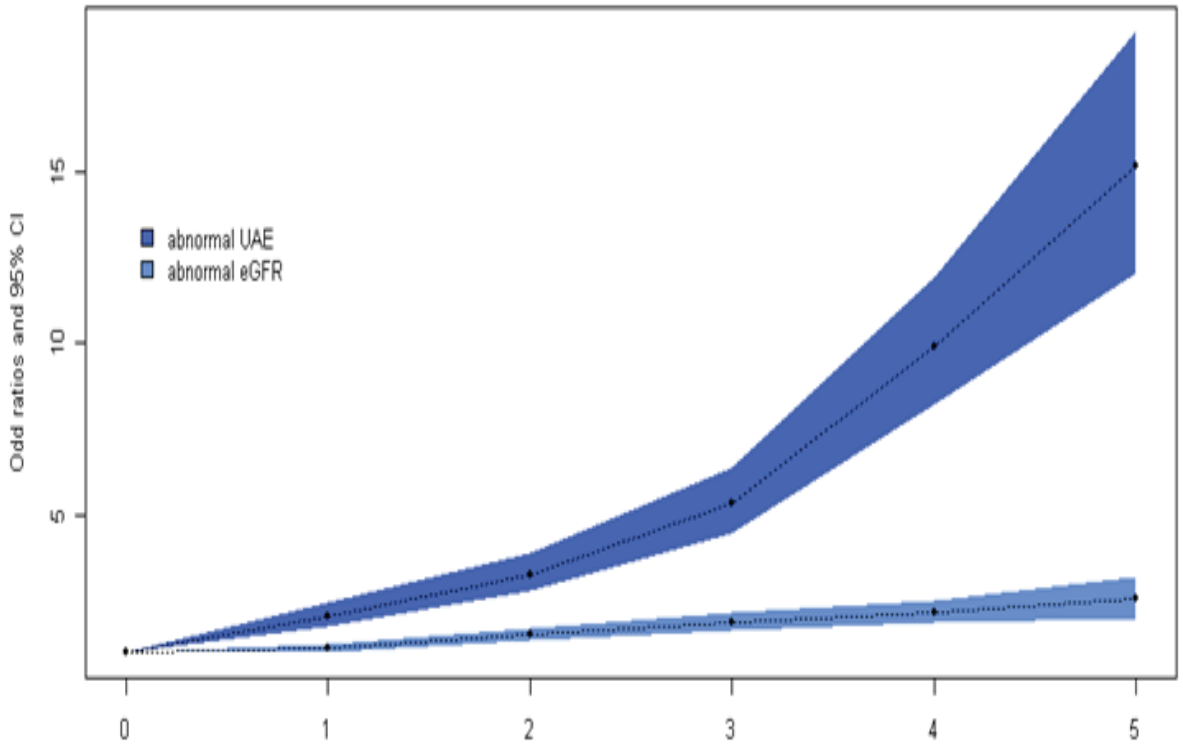
UAE : urinary albumin excretion. eGFR: estimated glomerular filtration rate

Figure 1 : Renal risk according to classes of body mass index. Age and gender adjusted odds ratios and 95% CI.



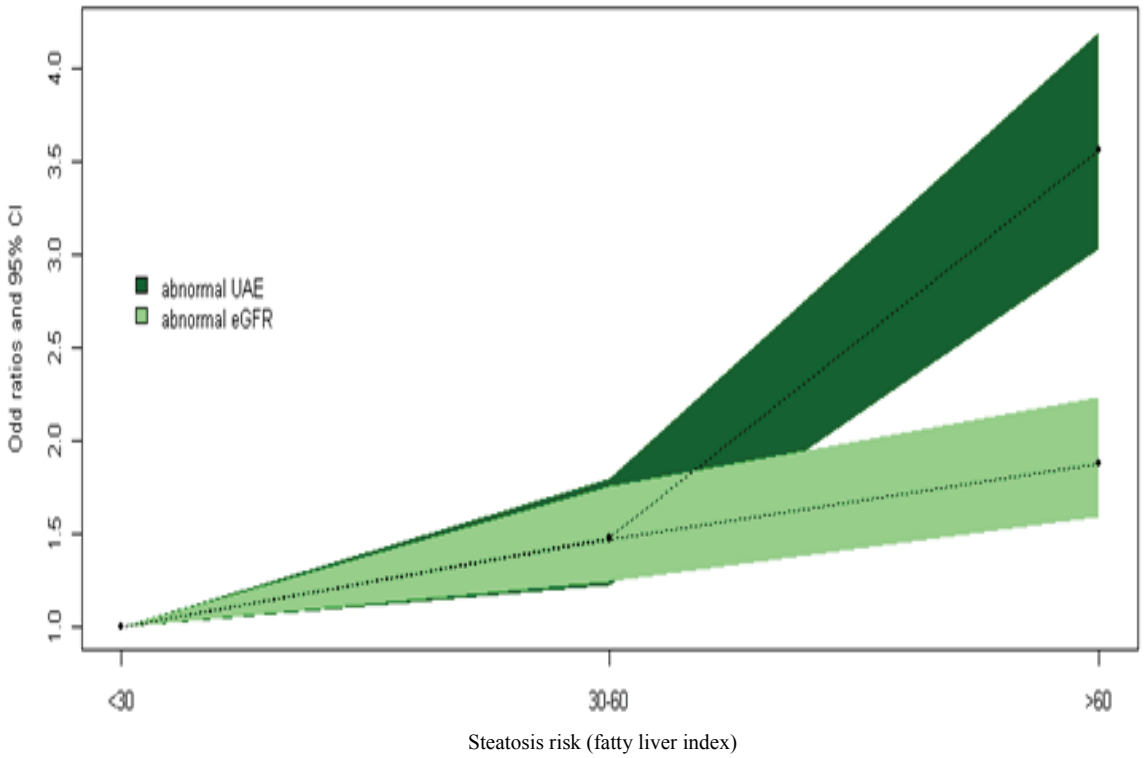
UAE: urinary albumin excretion. eGFR: estimated glomerular filtration rate.

Figure 2: Renal risk according to the number of components of the metabolic syndrome. Age and gender adjusted odds ratios and 95% CI.



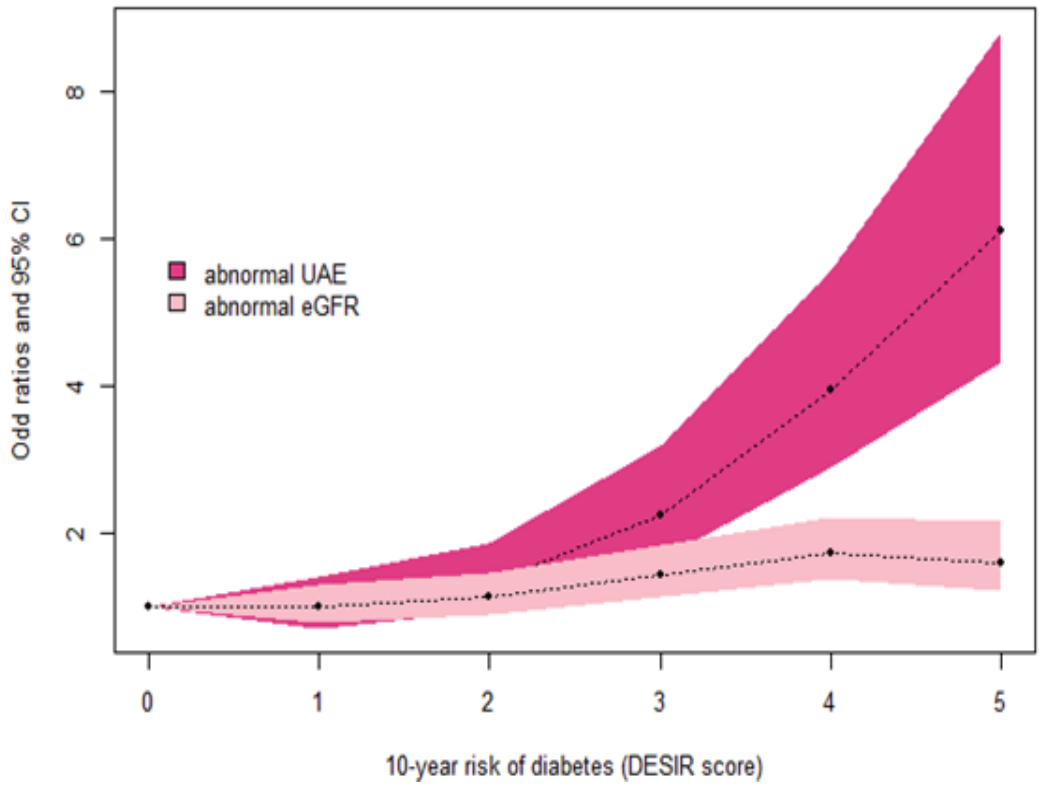
UAE : urinary albumin excretion. eGFR: estimated glomerular filtration rate.

Figure 3: Renal risk according to the steatosis risk, expressed with the Fatty Liver Index. Age and gender adjusted odds ratios and 95% CI.



UAE : urinary albumin excretion. eGFR: estimated glomerular filtration rate.

Figure 4 Renal risk according to the risk of incident diabetes, expressed with the DESIR score. Age and gender adjusted odds ratios and 95% CI.



UAE : urinary albumin excretion. eGFR: estimated glomerular filtration rate.

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24 pages – 5 tableaux – 4 figures

Abstract:

Introduction: Obesity and diabetes mellitus increase the risk of chronic renal disease. However, it is presently unknown whether all metabolic abnormalities, such as metabolic syndrome or nonalcoholic steatohepatitis are associated with impaired renal function, and whether they affect similarly albuminuria and glomerular filtration rate. Whether prediabetic state is associated with abnormal albuminuria before the occurence of diabetes is also unknown.

Methods: Large cross-sectional study in the general population.

Results: Overall, 118,314 subjects aged 40 years and over were included in the present study. Impaired renal function (abnormal albuminuria (≥30 mg/g) and/or low estimated glomerular filtration rate (eGFR<60 ml/min/1.73m²)) was observed in 5.3% of subjects. The association between body mass index (BMI) and abnormal albuminuria was a J-curve whereas the association with low eGFR was continuous. As compared to subjects with normal BMI, underweight subjects had a greater risk of abnormal albuminuria (OR: 2.12 [1.55-2.83]).

There was also a continuous relationship between the number of components of the metabolic syndrome and the risk of abnormal albuminuria or of low eGFR. However, the risk of abnormal albuminuria was much greater than the risk of low eGFR, for all metabolic disturbances. The presence of a high fatty liver index was a risk factor for abnormal albuminuria and for low eGFR. Finally, a high risk of developing diabetes was associated with elevated albuminuria, and to a lesser extent with low eGFR.

Conclusion: There is a J-curve relationship between BMI and abnormal albuminuria. Metabolic disturbances, such as metabolic syndrome and nonalcoholic steato-hepatitis, are associated with abnormal albuminuria, and to a lesser extent with low eGFR, suggesting a preferential association with endothelial dysfunction. Renal risk may precede the risk of diabetes mellitus.

Mots-clés : Chronic kidney disease
Albuminuria, Glomerular filtration rate
Metabolic syndrome, Lean subjects
Steatohepatitis, Risk of diabetes

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