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## Remission and progression of pre-existing micro- and macroalbuminuria over 15 years after bariatric surgery in Swedish Obese Subjects study

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### Introduction

Obesity can lead to renal disease and contribute to deterioration of kidney function.(1–3) Obesity-related cardiovascular disease, diabetes and hypertension also contribute to development of chronic kidney disease.(4–6) Several physiological mechanisms related to metabolic, hypertensive and local mechanical stress have been proposed to explain initiation and progression of obesity-related renal damage.(7–9) Obesity-related hyperglycemia increases glucose/sodium uptake in the proximal tubule which leads to reduced sodium delivery to the macula densa, triggering the tubuloglomerular feedback mechanism dilating the afferent arteriole and thereby increasing the glomerular filtration pressure.(7) Due to combination of RAAS activation(10–13) and a low-grade inflammatory response(14–16) in renal tissue, untreated obesity may result in glomerulomegaly, fibrotic response and

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Author contributions

JCAA and MT provided data collection and linkage with the Swedish authorities. MP and JCAA had access to and were responsible for acquisition and integrity of the data. AS was responsible for the statistical data analysis. All authors were responsible for interpretation of the data. AS and PAS drafted the manuscript. All authors participated in critical revision of the manuscript and provided intellectual input. LMSC, PAS, JCAA, KS and MT were involved in fundraising. All authors approved the final version and agreed to be accountable for all aspects of the work.

Conflicts of interest

CDS is employed by AstraZeneca. LMSC reports receiving consulting fees from Johnson&Johnson. CWIR serves on advisory boards for Novo Nordisk, GI Dynamics, Keyron, Herbalife, Boehringer Ingelheim, Johnson&Johnson, Sanofi, Consilient Health. Other authors report no conflicts of interest.

Supplementary data

Supplementary information is available at the International Journal of Obesity website.

impaired podocyte function, leading to glomerular lesions and structural changes, progressing proteinuria and ultimately to renal failure.(17–19)

In patients with obesity and earlier stages of renal disease, renal failure may take many years to develop. Increase in albuminuria is a well-established early surrogate marker of kidney disease progression.(19) More recently, estimated glomerular filtration rate decline (eGFR slope) has been accepted as a valid early surrogate endpoint for progression of renal disease towards renal failure and as a basis for potential approval of therapies for chronic kidney disease.(20, 21) An eGFR slope improvement of 0.5–1 ml/min/1.73m<sup>2</sup>/year over 2 years following a treatment was associated with a 30% lower risk of developing hard endpoints that included end-stage renal disease (ESRD).(20, 21)

Bariatric surgery results in long-term weight-loss and weight-maintenance, reduces long-term risk of cardiovascular events,(22) diabetes,(23, 24) its associated micro- and macrovascular complications(24–26) and ESRD.(27) Many studies have investigated the effects of bariatric surgery on variables related to kidney disease and function, e.g. urinary albumin excretion rate (U-AER), urinary albumin-to-creatinine ratio (U-ACR), estimated and measured glomerular filtration rates.(28) A recent meta-analysis of the effects of bariatric surgery on renal outcomes reports that albuminuria/proteinuria significantly improved after surgery.(29) Several smaller studies also demonstrated beneficial effects of bariatric surgery on remission of albuminuria in adolescent patients with diabetes mellitus(30) and adults.(31–38) Despite certain limitations in the population sizes and/or the follow-up times in the aforementioned studies, they indicate that bariatric surgery is associated with reduced albuminuria and improved glomerular filtration rates in patients with obesity and might facilitate remission of albuminuria. The physiological mechanisms that enable bariatric surgery to prevent progression and facilitate remission of pre-existing albuminuria are mainly unexplored but possibly linked to halting or reversal of the mechanisms that cause obesity-associated renal damage in the first place, e.g. glomerular hyperfiltration.

There is also evidence that medical treatment of obesity comorbidities, such as hypertension and diabetes, influences albumin excretion. Use of antihypertensive medication, e.g. ACE inhibitors(39) and ARB(39) and antidiabetic medication, e.g. DPP-4 inhibitors(40), GLP-1 receptor agonists(41, 42) and SGLT-2 inhibitors(43) has shown to reduce albuminuria.

Well-powered prospective studies of the long-term effects of bariatric surgery compared to conventional obesity care on changes in albuminuria and glomerular filtration rate decline in patients with pre-existing renal damage are currently scarce. In our earlier reports we demonstrated that bariatric surgery is associated with a long-term protection against albuminuria(44) and end-stage renal disease.(27) Here we report on the effects of bariatric surgery compared with conventional obesity care on remission and progression of pre-existing microalbuminuria, remission of macroalbuminuria and decline of estimated glomerular filtration rate over 15 years in the Swedish Obese Subjects (SOS) study.

## Subjects and methods

### Study design, data collection and definitions

The SOS study is an on-going prospective, controlled intervention study, which involves 25 public surgical departments and 480 primary health care units in Sweden. The study design has been accounted for in previous publications.(45, 46) The patients were recruited between 1 September 1987 and 31 January 2001. The patients were between 37 and 60 years old and had a BMI of at least 34 kg/m<sup>2</sup> for men and 38 kg/m<sup>2</sup> for women. In total, 4047 patients were included in this study. According to intention-to-treat principle, 2010 eligible patients who desired surgery constituted the surgery group and were treated with bariatric surgery. A matched control group of 2037 patients was created based on the data from the matching examination using 18 matching variables.(45) In the matched control group, patients were given conventional non-surgical obesity care at their primary health care centers.(47) The treatment of the control group was not pre-specified by the study protocol. All patients provided oral or written informed consent. Seven regional ethics review boards (Gothenburg, Lund, Linköping, Örebro, Karolinska Institute, Uppsala, Umeå) approved the study protocol. The study has been registered at [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01479452) (NCT01479452).

Physical examinations took place at baseline and after 0.5, 1, 2, 3, 4, 6, 8, 10, 15 and 20 years. At baseline and after 2, 10 and 15 years extended biochemical examinations were performed and analyzed at the Central Laboratory, Sahlgrenska University Hospital, Gothenburg, Sweden (accredited in accordance to European Norm 45001). These examinations included fasting blood samples and 24-hour urine samples, which patients collected according to detailed instructions. Use of antihypertensive and antidiabetic medications was self-reported in SOS questionnaires administered at baseline and at all SOS follow-up visits or obtained from the national register.

### Outcomes

The primary endpoint of the SOS study was overall mortality and power calculations were performed based on this outcome. Secondary endpoints included cardiovascular disease, diabetes and gall bladder disease. Albuminuria was not a predefined endpoint. Here we define albuminuria using urinary albumin excretion rate (U-AER) expressed in mg/24 hours and calculated based on the 24-hour urine collection using formula (1):

$$U-AER = \frac{\text{urine albumin concentration (mg/L)} \times \text{urine volume (L)}}{\text{urine collection time (min)} * 1440 \text{ min}} \quad (1)$$

Normoalbuminuria was defined as U-AER < 30 mg/24h. Albuminuria was defined as U-AER ≥ 30 mg/24h and was divided into microalbuminuria defined as 30 ≤ U-AER < 300 mg/24h, and macroalbuminuria defined as U-AER ≥ 300 mg/24h. Glomerular filtration rate (eGFR) was estimated using a four-term CKD-EPI formula(48) (with race term omitted).

### Study participants

The per protocol principle was applied in all analyses. Three patients who initially were assigned to the surgery group but have not proceeded with surgery were re-assigned to the control group. Hence, in the per protocol SOS study population 2007 patients constitute the

surgery group and 2040 patients constitute the control group. Baseline characteristics of the entire SOS study population are shown in Supplementary Table 1. Patients that were initially assigned to the control group but underwent bariatric surgery later in the study (n=380) were censored at the time of surgery. Patients that were initially assigned to the surgery group but underwent reversal to normal anatomy (n=91) were censored at the time of reversal. Patients with missing baseline U-AER values (18 control, 22 surgery) were censored at baseline. In the current analysis of remission and progression of micro- and macroalbuminuria defined by U-AER cutoff values, we thus include 803 patients (357 [or 17.5% of all] control; 446 [or 22.2% of all] surgery); of them 693 (312 [or 15.3% of all] control; 381 [or 19.0% of all] surgery) patients with microalbuminuria, and 110 (45 [or 2.2% of all] control; 65 [or 3.2% of all] surgery) patients with macroalbuminuria.

### Intervention

In the surgery group, 21% of microalbuminuria (n=79) and 11% of macroalbuminuria (n=7) patients were treated with banding; 66% of microalbuminuria (n=253) and 74% of macroalbuminuria (n=47) patients were treated with vertical banded gastroscopy; and 13% of microalbuminuria (n=49) and 15% of macroalbuminuria (n=11) patients were treated with gastric bypass. Control patients received conventional care offered at their primary health-care centers.(47) No attempts have been made to influence or standardize conventional care.

### Statistical analyses

Patients were followed up for as long as they stayed in the study and maximum for 15 years or were censored. Baseline characteristics were described using mean values with standard deviations, median values with interquartile ranges, or percent. Evaluation of baseline differences between the surgery and control groups were performed using two-sided *t*-tests for normally distributed continuous variables, non-parametric Mann-Whitney U-test for non-normally distributed continuous variables, Fisher's exact tests for categorical variables if  $n \leq 5$  and  $\chi^2$ -tests for categorical values if  $n > 5$ .

The overall differences in treatment effects between surgery and conventional care on changes in albuminuria and progression of eGFR decline during the entire follow-up period were analyzed using mixed effects models. Unadjusted U-AER values and changes in the latter along with unadjusted eGFR slopes were compared between the surgery and the control groups at baseline, 2, 10 and 15 years of follow-up using post-hoc non-parametric Mann-Whitney U-tests.

The difference in the total urinary albumin excretion for patients in the surgery group compared with patients in the control group was calculated based on area under the curve (AUC) of U-AER vs time. The AUC was used as a surrogate measure of total amount of excreted urinary albumin during a certain follow-up interval. At each time point, available U-AER data was used to calculate AUCs for each surgery and control patient. Fractions  $AUC_{surgery}/AUC_{control}$  between all possible pairs of surgery vs control patients were calculated and used to calculate differences in total urinary albumin excretion using formula (2).

$$\text{Difference in total urinary albumin excretion (\%)} = (1 - \text{AUC}_{\text{surgery}}/\text{AUC}_{\text{control}}) \times 100 \quad (2)$$

Remission and progression of microalbuminuria were calculated as proportions of the patients in surgery and control group that have achieved normoalbuminuria, or developed macroalbuminuria, respectively. Remission of macroalbuminuria was calculated as proportion of the patients in surgery and control group that have achieved micro- or normoalbuminuria. The effect of bariatric surgery compared to conventional care on prevalence of remission or progression of micro- and macroalbuminuria was compared between the surgery and the control groups using logistic regression at 2, 10 and 15 years of follow-up. Logistic regression with a single independent variable was used to calculate the odds ratio. Predictors for remission and progression were calculated using multivariable logistic regression models introducing co-variables for baseline gender, age, body mass index, pre-existing diabetes, systolic and diastolic blood pressure, serum insulin and natural log-transformed U-AER. At all follow-up time points, adjustment for use of medication with potential to influence urinary albumin excretion was performed.

Statistical significance was defined as  $p < 0.05$  for two-tailed p-values. Calculations were performed using IBM SPSS Statistics v 24 and STATA v 16.1.

## Results

### Baseline characteristics

Patients in the surgery group with micro- or macroalbuminuria, both combined and separately, had similar U-AER values at baseline compared with corresponding control patients. Patients with pre-existing U-AER albuminuria (micro- and macroalbuminuria combined) in the surgery group had a slightly worse metabolic profile with higher baseline mean values for body weight, BMI, serum levels of insulin, homeostatic model assessment of insulin resistance (HOMA-IR), and systolic and diastolic blood pressure, compared with the control group (Table 1A). These patients were also slightly younger and had marginally higher baseline eGFR, although mean eGFR values in both surgery and control groups suggest that the study patients had in general good glomerular filtration rates. Similar baseline differences were seen between the surgery and control groups for patients with only microalbuminuria (Table 1B). In patients with macroalbuminuria only differences in systolic blood pressure and eGFR reached statistical significance (Table 1C).

No baseline differences in use of antihypertensive medication (ACEi and/or ARB) or antidiabetic medication (DPP-4 inhibitors and/or GLP-1 analogues and/or SGLT-2 inhibitors) were observed between the surgery and control group (Supplementary Table 2).

### Change in pre-existing micro- and macroalbuminuria

In patients with albuminuria (micro- or macroalbuminuria combined), a decline in median U-AER values over the entire follow-up period was observed in the surgery group. This decline was greater compared with the corresponding control group (Figure 1A). Similar results were obtained when patients with microalbuminuria were analyzed separately (Figure

1B). For patients with macroalbuminuria, the difference between surgery and control groups was observed only after 2 years of follow-up (Figure 1C).

In patients with albuminuria (Figure 2A) or microalbuminuria only (Figure 2B) there was a larger decrease in the U-AER in the surgery group compared to the control group during the entire follow-up period. For patients with macroalbuminuria, there was a larger decrease in average U-AER after 2 years of follow-up in the surgery group compared with the control group, while there was a similar decrease after 10 and 15 years of follow up in both treatment groups (Figure 2C).

Total urinary albumin excretion in patients with albuminuria (micro- and macroalbuminuria combined) was 22.2% smaller (95% CI 21.5–22.9) after 2 years, 35.2% smaller (95% CI 34.1–36.1) after 10 years and 36.5% smaller (95% CI 34.8–38.1) after 15 years in the surgery group compared with the control group, based on median difference between the groups. When analyzed separately, total urinary albumin excretion in the surgery group compared with the control group was 24.0% smaller (95% CI 23.4–25.5) after 2 years, 42.8% smaller (95% CI 41.9–43.7) after 10 years and 44.5% smaller (95% CI 43.0–46.2) after 15 years of follow-up, and 27.8% smaller (95% CI 22.0–32.9) after 2 years of follow-up in patients with macroalbuminuria, based on median difference between the groups. Differences in total urinary albumin excretion were not observed in the surgery group compared with the control group in patients with macroalbuminuria after 10 and 15 years of follow-up.

### Remission and progression of pre-existing microalbuminuria

The unadjusted proportion of the patients in remission was higher in the surgery group compared with the control group after 2, 10 and 15 years of follow-up (Figure 3A), and remained higher after multivariate adjustments for baseline parameters (Supplementary Table 3). Higher baseline U-AER was associated with lower chance of remission during the entire follow-up. At 10 and 15 years an association between male sex and lower chance of remission was observed (Supplementary Table 3).

The unadjusted proportion of patients with progression was lower in the surgery group compared with the control group after 2, 10 and 15 years of follow-up (Figure 3B), and remained lower after multivariate adjustments (Supplementary Table 4). Higher baseline U-AER was associated with a greater risk of progression during the entire follow-up. Once again, male sex was associated with higher risk of progression to macroalbuminuria at 15 years (Supplementary Table 4).

Use of ACEi and/or ARB in patients with microalbuminuria was higher in the control group after 10 and 15 years of follow-up (Supplementary Table 2). Use of DPP-4 inhibitors and/or GLP-1 analogues and/or SGLT-2 inhibitors was higher in the control group after 15 years of follow-up. After adjustment for the use of the aforementioned medication, the proportion of patients in remission to normoalbuminuria remained higher and the proportion of patients in progression to macroalbuminuria remained lower in the surgery group compared with the control group during the entire follow-up period.

Patients treated with gastric bypass had the highest chance of remission at 2 and 10 years and at 15 years all patients with pre-existing microalbuminuria, who were treated with gastric bypass, were in remission (Supplementary Table 5A). Moreover, no patient with microalbuminuria, who was treated with gastric bypass, progressed to macroalbuminuria at any time point in this study (Supplementary Table 5B).

### Remission of pre-existing macroalbuminuria

The unadjusted proportion of the patients in remission after 2 years was higher in the surgery group compared with the control group (Figure 3C), and remained higher after multivariate adjustments for baseline parameters (Supplementary Table 6). Higher baseline U-AER was associated with lower chance of remission at 2 years. The proportion of surgery patients in remission was similar in the control and surgery groups after 10 and 15 years of follow-up.

The use of ACEi and/or ARB in patients with macroalbuminuria was higher in the surgery group after 2 years of follow-up (Supplementary Table 2). The proportion of patients in remission in the surgery compared with the control group at 2 years remained higher after adjustments for use of ACEi and/or ARB after 2 years of follow-up.

### Progression of eGFR decline

Decline in eGFR was observed both in the surgery and in the control group during the entire follow-up (Figure 4). A slower progression of eGFR decline was observed after 2 years in all surgery patients with pre-existing albuminuria (treatment effect: 1.1 ml/min/1.73m<sup>2</sup>/year, 95% CI 0.5–1.6,  $p=0.001$ ) and separately in surgery patients with microalbuminuria (treatment effect: 1.0, 95% CI 0.4–1.6,  $p=0.001$ ) and macroalbuminuria (treatment effect: 1.4 ml/min/1.73m<sup>2</sup>/year, 95% CI 0.0–2.9,  $p=0.047$ ), compared with corresponding control patients (Table 2). No differences in rates of eGFR decline were observed between surgery and control patients at later follow-up times, over the entire follow-up, or between surgery patients with different levels of albuminuria or eGFR at baseline.

## Discussion

We have shown that in patients with pre-existing microalbuminuria, total urinary albumin excretion was reduced after bariatric surgery compared with conventional obesity care over up to 15 years of follow-up. Furthermore, bariatric surgery facilitated long-term remission to normoalbuminuria and prevented long-term progression to macroalbuminuria compared with conventional care.

Increase in albuminuria is a well-established surrogate marker for the progression of chronic kidney disease, particularly in patients with albuminuria.(49) Several studies have shown association between bariatric surgery and remission from microalbuminuria, with up to 50% of patients in remission after 1 year of follow-up(35) and even higher remission rates after 10 years of follow-up.(36) Generally, results from our study were in line with and extend previous studies(29, 31–37) by providing a well powered analysis of long-term remission rates of microalbuminuria. Together, these studies suggest that remission from microalbuminuria is relatively common and a long-lasting effect of bariatric surgery.

Nevertheless, some patients undergoing surgical treatment may still have progressive kidney disease. We have shown that for patients with microalbuminuria that undergo bariatric surgery, reduced risk of progression of pre-existing albuminuria is also a potential long-term benefit of this treatment.

Gastric bypass is associated with high chance of remission of microalbuminuria.(35, 37) In our study, during the entire follow-up time of 15 years, 87.5–100% of the patients treated with gastric bypass achieved remission of microalbuminuria to normoalbuminuria. Additionally, none of the patients with pre-existing microalbuminuria, who were treated with gastric bypass, progressed to macroalbuminuria at any time point in this study.

Bariatric surgery has previously been shown to facilitate remission of macroalbuminuria in adolescents with obesity and diabetes mellitus.(30) Our analysis of protective renal effects of bariatric surgery in adult patients with pre-existing macroalbuminuria extends previous studies and is, to the best of our knowledge, the most comprehensive to date on this subject. In patients with pre-existing macroalbuminuria, total urinary albumin excretion was lower and remission to normo- or macroalbuminuria was higher after 2 years following bariatric surgery compared with conventional obesity care, but these effects were short-term.

We have shown clinically significant improvements in rate of eGFR decline after 2 years following bariatric surgery compared with conventional care, suggesting that bariatric surgery can prevent progression of kidney dysfunction towards renal failure in patients with micro- and macroalbuminuria.(21) We did not observe any differences in eGFR decline past the 2-year point, the reasons behind this discrepancy are unclear but might be due to high variability in the variable under examination, insufficient number of patients and the very low sampling frequency over the longer time periods.

One limitation of the SOS study is the fact that the groups were not randomized. This design was necessary for ethical reasons given the high postoperative death rate (1–5%) following bariatric surgery at the time the study was initiated in 1987. Furthermore, the study was not originally designed to investigate the effects of bariatric surgery on progression or remission of U-AER based albuminuria, progression of eGFR decline or physiological mechanisms behind these effects. The physiological mechanisms behind positive effects of bariatric surgery on surrogate and hard renal endpoints still need to be explained. Albuminuria was neither an inclusion criterion nor a pre-defined endpoint, and only 20% of the total SOS population were included in current study. The power of the analysis of the long-term effects of bariatric surgery in patients with macroalbuminuria was limited due to the low number of patients past the 2-year point, and the results of this analysis should be interpreted with caution. Calculations of U-AER were based on single values for urinary albumin concentrations, and this parameter can vary from day to day. Some studies indicate that number of urine collections over time does not change the average medical treatment effect estimate but merely enhances statistical power.(50) Therefore, the changes observed in this study has been observed despite a low number of observations and not due to an uncertain sampling methodology. Furthermore, collection of albumin excretion over 24 hours as in this trial would be assumed a more robust measurement than an ordinary untimed spot urine sample.



We also need to assume that regression towards the mean has somewhat influenced results, which would lead to overestimation of remission in albuminuria in the individual treatment groups. In this case both surgery and control groups are likely to be affected, but not the differences between these groups. The major strengths of the SOS study are the large population and the length of the follow-up time. The latter is particularly important since renal disease is a late complication of obesity and obesity related disorders and may take many years to develop, as shown in our previous study on end stage kidney disease in the SOS study.(27)

In conclusion, bariatric surgery reduces urinary albumin excretion and facilitates remission of albuminuria independently of the use of antihypertensive and antidiabetic medications with potential to reduce urinary albumin excretion. Moreover, bariatric surgery shows the potential to reduce the progression rate of estimated glomerular filtration decline. These findings are in line with previously observed reductions in the progression towards end stage renal disease after bariatric surgery.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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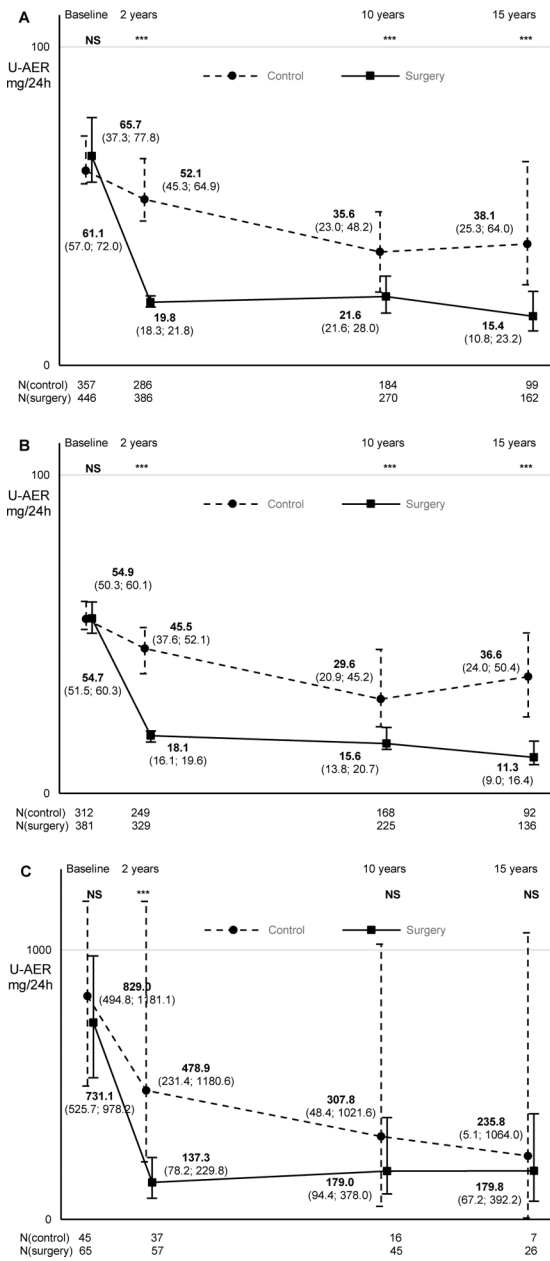
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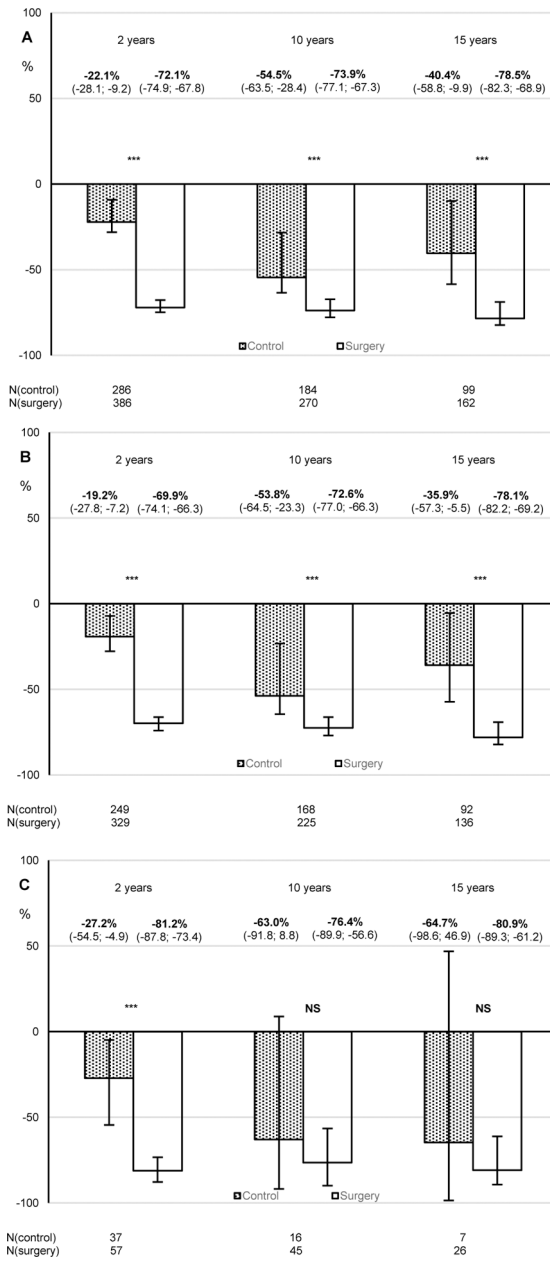
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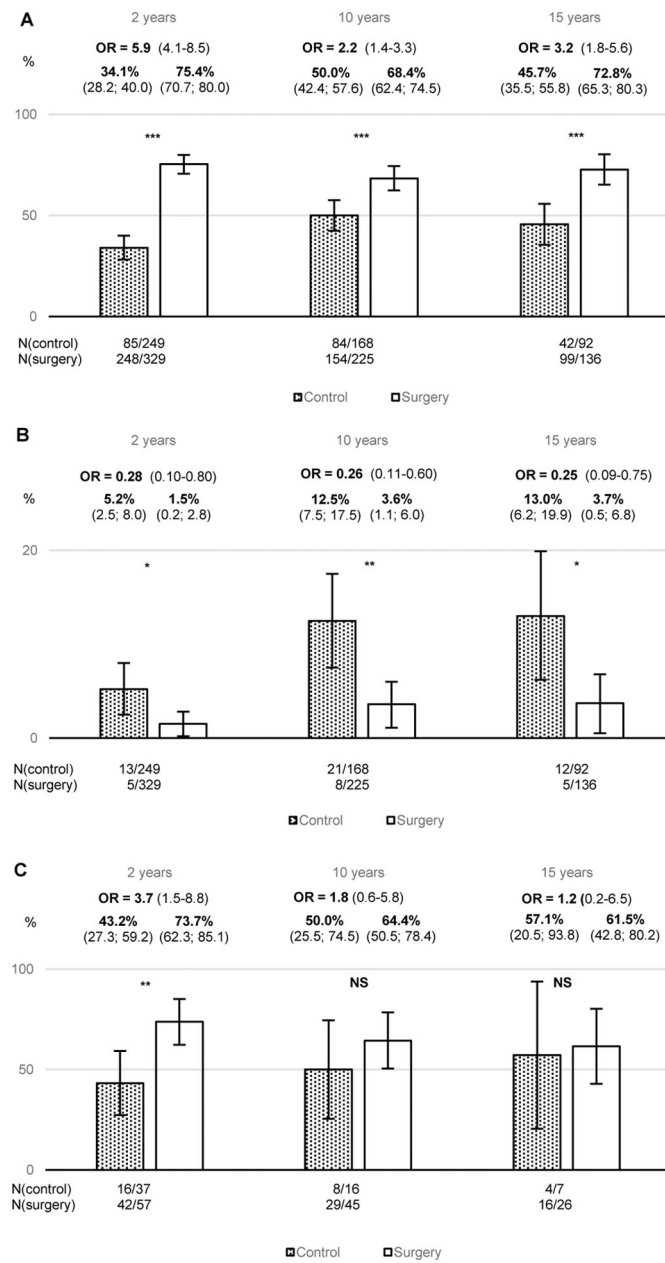
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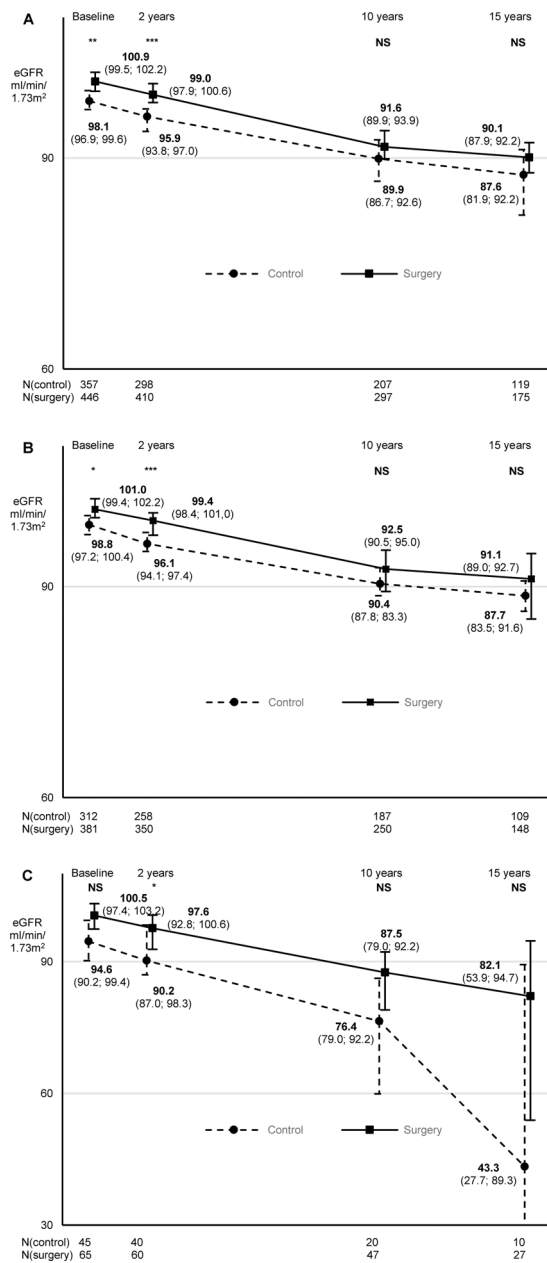
**Figure 1.** Median U-AER for A) all patients with pre-existing albuminuria, B) patients with microalbuminuria and C) patients with macroalbuminuria. Number of patients with available data analyzed at each time point is displayed below the graph. Error bars and values in brackets represent 95% CI. Statistical significance in differences between surgery and control groups are marked with asterisks, where \* indicates  $p$  0.05, \*\* indicates  $p$  0.01, \*\*\* indicates  $p$  0.001 and NS indicates no statistical significance.



**Figure 2.** Median change in U-AER in percent from baseline for A) all patients with pre-existing albuminuria, B) patients with microalbuminuria and C) patients with macroalbuminuria. Number of patients with available data analyzed at each time point is displayed below the graph. Error bars and values in brackets represent 95% CI. Statistical significance in differences between surgery and control groups are marked with asterisks, where \* indicates  $p < 0.05$ , \*\* indicates  $p < 0.01$ , \*\*\* indicates  $p < 0.001$  and NS indicates no statistical significance.



**Figure 3:** Prevalence of A) remission to normoalbuminuria and B) progression to macroalbuminuria in patients with microalbuminuria; C) remission to normo- or microalbuminuria in patients with macroalbuminuria. Albuminuria is defined by U-AER cutoff values. Odds ratios (ORs) are unadjusted and calculated using logistic regression analysis. Error bars and values in brackets represent 95% CI. Numbers of events vs numbers at risk are displayed below the graph. Statistical significance in differences between surgery and control groups are marked with asterisks, where \* indicates  $p$  0.05, \*\* indicates  $p$  0.01, \*\*\* indicates  $p$  0.001 and NS indicates no statistical significance.



**Figure 4.** Median eGFR estimated with four-term CKD-EPI formula for A) all patients with pre-existing albuminuria, B) patients with microalbuminuria and C) patients with macroalbuminuria. Number of patients with available data analyzed at each time point is displayed below the graph. Error bars and values in brackets represent 95% CI. Statistical significance in differences between surgery and control groups are marked with asterisks, where \* indicates  $p$  0.05, \*\* indicates  $p$  0.01, \*\*\* indicates  $p$  0.001 and NS indicates no statistical significance. The y-axis has been adapted to represent CKD cut-off levels.



**Table 1.**

Baseline characteristics of study patients showing mean values with standard deviations or median values with interquartile ranges, where applicable. A) All patients with pre-existing albuminuria (micro- and macroalbuminuria combined); B) patients with microalbuminuria and C) patients with macroalbuminuria. Statistical significance in differences between surgery and control groups are marked with asterisks, where \* indicates p 0.05, \*\* indicates p 0.01, \*\*\* indicates p 0.001 and NS indicates no statistical significance.

	A) Patients with pre-existing albuminuria (micro- and macroalbuminuria combined).			B) Patients with microalbuminuria.			C) Patients with macroalbuminuria.		
	Control	Surgery	p-value	Control	Surgery	p-value	Control	Surgery	p-value
<b>N=</b>	357	446		312	381		45	65	
Age, years, mean	48.4±6.3	47.2±5.7	**	48.3±6.3	47.0±5.7	**	49.3±6.3	48.4±5.9	NS
Male gender, %	41.7	58.8	NS	38.5	45.9	NS	64.4	53.8	NS
Weight, kg, mean	119.7±18.8	125.9±18.2	***	119.1±18.6	125.2±18.0	***	123.6±19.9	129.9±19.0	NS
BMI, kg/m <sup>2</sup> , mean	41.0±5.2	42.5±4.8	***	41.0±5.1	42.4±4.8	***	41.5±5.4	43.0±4.7	NS
Diabetes, %	27.5	33.0	NS	26.6	31.0	NS	33.3	44.6	NS
Blood glucose, mmol/L, mean	5.9±2.7	6.0±2.6	NS	5.8±2.6	5.9±2.5	NS	6.7±3.1	6.7±3.2	NS
Serum insulin, mU/L, mean	22.8±13.4	25.9±15.7	**	22.0±11.5	25.7±15.6	***	28.6±21.7	27.1±16.4	NS
HOMA-IR, a.u., mean	6.3±5.6	7.1±5.9	**	5.9±4.6	6.9±5.5	**	9.1±9.4	8.4±7.7	NS
SBP, mmHg, mean	145.5±19.1	152.8±20.9	***	144.8±18.2	151.3±20.3	***	150.0±23.9	161.6±22.5	**
DBP, mmHg, mean	89.9±11.8	93.9±12.2	***	89.7±11.5	93.5±11.9	***	91.5±13.6	96.6±13.2	NS
U-AER, mg/24h, median	61.1 (41.4; 141.2)	65.7 (39.6; 144.9)	NS	54.7 (39.4; 94.5)	54.9 (38.0; 96.3)	NS	829.0 (407.1; 1399.1)	731.1 (427.6; 1313.7)	NS
eGFR, ml/min/1.73m <sup>2</sup> , median	98.1	100.9	**	98.8	101.0	*	94.6	100.5	NS
IQR	(89.9; 105.1)	(92.5; 106.9)		(90.5; 105.2)	(93.1; 106.9)		(82.0; 103.7)	(90.5; 106.4)	
CKD stage, %									
0-1	74.5	81.8	**	75.6	82.7	**	66.7	78.5	NS
2	24.4	18.2		24.0	17.3		26.7	21.5	
3	1.1	0.0		0.4	0		6.6	0	

BMI = body mass index; HOMA-IR = homeostasis model assessment of insulin resistance; SBP = systolic blood pressure; DBP = diastolic blood pressure; U-AER = Urinary albumin excretion rate; IQR = interquartile range; LN U-AER = natural log-transformed U-AER; eGFR = estimated glomerular filtration rate according to four-term CKD-EPI formula; CKD = chronic kidney disease; IQR = interquartile range.

**Table 2.**

Rates of progression of eGFR decline (eGFR slopes), expressed in ml/min/1.73m<sup>2</sup>/year after 2, 10 and 15 years of follow-up, showing median values with 95% CI for A) All patients with pre-existing albuminuria (micro- and macroalbuminuria combined); B) patients with microalbuminuria and C) patients with macroalbuminuria. Statistical significance in differences between surgery and control groups are marked with asterisks, where \* indicates p 0.05, \*\* indicates p 0.01, \*\*\* indicates p 0.001, NS indicates no statistical significance.

A	Control	Surgery	<i>p</i> -value	B	Control	Surgery	<i>p</i> -value	C	Control	Surgery	<i>p</i> -value
N (2 years)	298	410		N (2 years)	258	350		N (2 years)	40	60	
eGFR slope 0-2 years (ml/min/1.73m <sup>2</sup> /year)	-1.6	-0.6		eGFR slope 0-2 years (ml/min/1.73m <sup>2</sup> /year)	-1.5	-0.6		eGFR slope 0-2 years (ml/min/1.73m <sup>2</sup> /year)	-2.1	-0.6	
95% CI	(-2.0; -1.2)	(-0.8; -0.3)		95% CI	(-1.8; -1.1)	(-0.9; -0.3)		95% CI	(-3.7; -1.1)	(-2.0; 0.3)	
Treatment effect	1.1			Treatment effect	1.0			Treatment effect	1.4		
(ml/min/1.73m <sup>2</sup> /year)			***	(ml/min/1.73m <sup>2</sup> /year)			***	(ml/min/1.73m <sup>2</sup> /year)			*
95% CI	(0.5; 1.6)			95% CI	(0.4; 1.6)			95% CI	(0.0; 2.9)		
N (10 years)	207	297		N (10 years)	187	250		N (10 years)	20	47	
eGFR slope 0-10 years (ml/min/1.73m <sup>2</sup> /year)	-1.0	-1.0		eGFR slope 0-10 years (ml/min/1.73m <sup>2</sup> /year)	-0.9	-0.9		eGFR slope 0-10 years (ml/min/1.73m <sup>2</sup> /year)	-1.3	-1.6	
95% CI	(-1.2; -0.8)	(-1.1; -0.9)		95% CI	(-1.1; -0.7)	(-1.1; -0.8)		95% CI	(-2.3; -0.6)	(-2.1; -1.2)	
Treatment effect	0.1			Treatment effect	0.1			Treatment effect	-0.2		
(ml/min/1.73m <sup>2</sup> /year)			NS	(ml/min/1.73m <sup>2</sup> /year)			NS	(ml/min/1.73m <sup>2</sup> /year)			NS
95% CI	(-0.1; 0.4)			95% CI	(-0.2; 0.3)			95% CI	(-1.0; 0.7)		
N (15 years)	119	175		N (15 years)	109	148		N (15 years)	10	27	
eGFR slope 0-15 years (ml/min/1.73m <sup>2</sup> /year)	-0.8	-0.8		eGFR slope 0-15 years (ml/min/1.73m <sup>2</sup> /year)	-0.8	-0.8		eGFR slope 0-15 years (ml/min/1.73m <sup>2</sup> /year)	-2.5	-1.8	
95% CI	(-1.1; -0.7)	(-1.0; -0.7)		95% CI	(-1.0; -0.7)	(-1.0; -0.7)		95% CI	(-5.3; -1.5)	(-2.9; -0.8)	
Treatment effect	0.1			Treatment effect	0.1			Treatment effect	0.7		
(ml/min/1.73m <sup>2</sup> /year)			NS	(ml/min/1.73m <sup>2</sup> /year)			NS	(ml/min/1.73m <sup>2</sup> /year)			NS
95% CI	(-0.2; 0.3)			95% CI	(-0.2; 0.3)			95% CI	(-0.4; 1.9)		