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Running head: Medication use after RYGB

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Abstract

Objective: To determine the influence of Roux-en-Y gastric bypass (RYGB) on medication-related costs.

Methods: Analysis of types, dosages and costs of drugs and medical devices prescribed before and after surgery (1, 3, 6, 12 months and yearly thereafter) in patients who underwent RYGB between June 2004 and May 2010, and had an outpatient visit between December 2009 and May 2010 at Pitié-Salpêtrière University Hospital, Paris, France.

Results: The cohort included 143 patients (78% female, mean age 42.9 years, mean BMI 48.6 kg/m²). Total prescription costs were significantly lower (-32%, $p<0.001$) one year after RYGB compared with preoperative costs. However, the cost for medications to prevent RYGB side effects (in particular nutritional deficiencies) displayed a 36-fold increase in the first month post-surgery, but then decreased progressively over time. Importantly, the cost related to the treatment of the two most frequent obesity-related diseases significantly decreased one year after surgery. Indeed, prescription costs for treatment of type 2 diabetes (T2D) and obstructive sleep apnea (OAS) (namely CPAP therapy considered as the gold standard treatment) were reduced one year after surgery by 85% and by 63% (both $p<0.001$), respectively. We also observed a trend toward a decrease in the prescription costs of other obesity-related diseases, although it didn't reach significance in our cohort.

Conclusions*:* Considering medication to treat both obesity-related diseases and prevention of secondary effects of bariatric surgery, we observed that overall post-operative medication costs were significantly reduced one year after surgery, especially for T2D and OSA.

Abstract words: 244

Keywords: Medication cost – Prescriptions – Obesity – Comorbidities - Bariatric surgery – Roux-en-Y gastric bypass

Introduction

The prevalence of obesity has increased worldwide over the last decades [1], thereby also increasing the prevalence of obesity-related diseases (such as type 2 diabetes mellitus (T2D), dyslipidemia, hypertension, cardiovascular diseases (CVD), but also obstructive sleep apnea (OSA), asthma, joint arthritis, and depression) [2]. Therefore, obese individuals are prone to increased consumption of drugs compared to lean individuals [3].

Medical management of obesity has proven disappointing on both the amount of weight loss and its maintenance over time [4]. Therefore, the number of patients undergoing bariatric surgery such as Roux-en-Y gastric bypass (RYGB), which is indicated for the most severe form of obesity, has increased dramatically. Most importantly, it is currently the only efficient mean to achieve major and sustainable weight reduction [2,5]. Along with a significant reduction in all-cause mortality, RYGB improves several obesity-related diseases [6-10], leading to a decreased consumption of related treatments [11]. Indeed, medication used for T2D, hypertension and dyslipidemia decreased significantly as early as 1 year post-surgery (by 76%, 51% and 59%, respectively) [12]. This reduction continued significantly 3 years post-surgery, in particular for T2D, dyslipidemia and CVD [11]. Finally, comparing obese patients post-surgery to an obese matched control group, the SOS study, demonstrated a significant reduction in the cost of drugs for obesity-related diseases after 7 years, which remained significantly lower during 20 years of follow-up [13].

Although beneficial regarding mortality and obesity-related comorbidities, RYGB induces potential risks such as nutritional deficiencies and short term surgical complications such as venous thrombosis, anastomosis ulceration and gallstones [16-18].

Both can be prevented by specific drug prescriptions such as daily vitamin and mineral substitution [14,15], hence inducing substantial costs. Few studies (if any) have yet addressed the overall treatment cost evolution after surgery taking into account not only treatment of

obesity-related diseases but also surgery side effects' prevention. As it remains unclear to what extent RYGB may be cost-saving in terms of overall drug consumption, we aimed to examine the evolution of medication use and associated costs in RYGB patients.

Methods and procedures

Study design and data collection

We took advantage of an ongoing clinical research protocol (approved by the Ethics Committee of Hôtel-Dieu Hospital) including all of our bariatric surgery patients followed at the Nutrition Department of Pitié-Salpêtrière hospital Paris, France. All subjects gave written informed consent. Only those who underwent RYGB were included. Bariatric surgery was decided in agreement with international clinical practice guidelines [19]. For the purpose of the study, patients who had undergone a previous bariatric surgery, as well as those who didn't attend postoperative follow-up, were excluded.

We first retrospectively included all patients who had undergone RYGB from June 2004 to November 2009, and for whom clinical data (age, sex, BMI) were available in our database both before (baseline) and 1, 3, 6 months (M) and yearly (Y) after surgery, until 4 years post-RYGB, and who had a follow-up visit. We also prospectively included patients who came for a RYGB preoperative examination between December 2009 and May 2010. Data were collected from patient's medical records and verified with the patient at the inclusion visit. Entire obesity-related diseases history and complete list of drugs and medical devices prescribed at each examination (including Continuous Positive Airway Pressure (CPAP), considered as the gold standard treatment of OSA) [20] was retrieved. The dosing regimen for each drug was also collected.

Data analysis

We tabulated drugs taken by each patient at each follow-up time point, including cost per month (in euros). The cost for each medication or medical device was obtained from the

official current price list (http://www.theriaque.org and www.ameli.fr) and when appropriate, generic drug costs for the largest package available, were used. Treatments were divided into curative use (further grouped according to the different obesity-related diseases they were used for (including CPAP treatment)), or preventive use (those to prevent surgery-related complications or potential nutritional deficiencies). The different categories of obesity-related diseases were defined upon medication use and thorough checking of the adequacy with each patient's medical history. Patients with T2D were defined as those on oral anti-diabetic therapy and/or insulin and/or GLP-1 analogue. OSA included patients on CPAP treatment. CVD comprised antihypertensive drugs and/or antiplatelet agents and included secondary CVD prevention drugs. Dyslipidemia included patients treated with statin or fibrates. Psycho- and neurological disorders comprised patients who were on antidepressant therapy and those with anti-epileptic treatment. Lastly, a category called "other" included patients using pain killers, drugs used for asthma, hyperuricemia, skin complications, urinary incontinence or gastrointestinal problems.

We used the Anatomical Therapeutic Chemical classification system (ATC-system), which categories drugs into different classes according to their therapeutic and chemical characteristics, at the first level, except for drugs used in metabolic disorders, which were classified at level 2 of the ATC-system (http://www.whocc.no/). Prevention treatment at our center has previously been described [13] and includes 2 weeks before surgery: vitamin D (once 4x100000IU), vitamin B1 (250mg/day), vitamin B12 (250µg/day) and esomeprazole (40mg/day). Esomeprazole dosing is maintained during 6 months post-surgery to prevent anastomosis ulcerations. Enoxaparine (4000IU 1inj/day) is prescribed for 3 weeks post-surgery to prevent venous thrombosis. Fifteen days post-RYGB, vitamin and mineral supplements including Azinc optimal® (2x/day), iron (2x80mg/day), vitamin D (800IU/day) and calcium (1000mg/day) are started and continued on the long term. Ursodeoxycholic acid

is introduced 2 weeks post-surgery (only for patients with no previous history of cholecystectomy) and continued for 3 months to prevent gallstone formation known to be associated with major and rapid weight loss [16-19]. Besides this standard protocol, additional drugs and/or supplements to treat side effects related to surgery (vitamins, minerals and proteins, antiemetics,…) can be added on an individually-tailored basis.

Statistical analysis

Continuous variables are presented as mean±SD. The main outcome variables were the changes in the relative cost of each comorbidity treatment, calculated both in the whole cohort or considering only those patients affected with the comorbidity in question. Changes in (i) the total cost and (ii) the medication cost for both preventive and curative use were evaluated. Medication costs 1, 3, 6, 12, 24, 36 and 48 months after RYGB were compared with those at baseline. Two-way ANOVA and Chi-^{2} tests were used. Statistical significance was set at $p < 0.05$.

Results

We included 143 patients whose characteristics are displayed in Table 1. BMI gradually decreased during the first year post-RYGB and then stabilized up to four years (48.6±9 kg/m^2 vs. 33.2±8 kg/m^2) (Figure 1) (ie: mean weight loss 33±18 kg).

When compared to baseline values, we observed a significant 32% reduction in the total prescription costs one year post-surgery ($p<0.01$) (Figure 2). Curative medications and medical device cost significantly decreased as early as one month post-surgery and onwards (Figure 3). The most significant reduction in the mean prescription cost concerned T2D and OSA treatments (Table 2). Indeed, 34% of patients were treated for T2D at baseline, which was reduced respectively to 16%, 11%, 9% and 0%, after 3 months, 1, 2 and 4 years after RYGB. Likewise, T2D treatment cost decreased by 65% ($p<0.01$) at 1 month, and further over time to reach 0€ four years post-RYGB (Table 3).

OSA mean treatment cost decreased significantly as early as 3 months post-surgery and onwards to reach its lowest cost (12.86€/month) at three years (ie: 89% reduction vs. baseline). By contrast, drugs for CVD and dyslipidemia's cost decreased more weakly (-51.5% and -81%, respectively), only reaching significance one and two years post-RYGB. We observed no significant change regarding other obesity-related disease prescriptions.

As expected, preventive treatment's prescription just before the surgery induced a 36 fold increase in the cost one month post-surgery, compared with baseline. Although this cost decreased over time, but it remained significantly higher than baseline values, even after four years.

Discussion

This study aimed to investigate the overall medication costs after RYGB. We focused both on the costs of the different obesity-related diseases treatments, and those of treatments prescribed to prevent surgery-related complications, and observed a significant reduction in the global medication cost one year post-surgery and onwards, compared with baseline. This major post-surgery cost reduction was mainly explained by the acute decrease in T2D and OSA treatment prescriptions.

The marked reduction in T2D medication use observed in our study, resulted in an 85 fold decrease in medication cost one year post-RYGB among the patients with diabetes, which is in line with previous pharmaco-economic studies. Segal *et al* [12] evaluated medication use in 6,235 patients undergoing bariatric surgery and demonstrated 76% reduction in T2D medication use one year post-surgery that persisted up to four years [22]. A significant reduction in oral anti-diabetic agents and insulin therapy (80% and 79%) four years post-RYGB was also observed in another study, including 191 diabetic patients [23]. Although our cohort was of a smaller size, the reduction of T2D treatment is in line with a significant improvement or normalization of both HBA1c and fasting glycemia during follow-up.

Literature entails that RYGB enables (i) a 57.5% T2D remission [24] according to the definition [25], (ii) an 84% improvement in T2D status [26], and (iii) a reduction in the occurrence of T2D [27]. We herein demonstrate a significant cost reduction as soon as one month post-RYGB, in agreement with the rapid improvement of diabetes post-surgery which involves multiple mechanisms [28-30], some unrelated to weight loss [23,28,31].

OSA occurred in 33% of our patients at baseline. We observed a 63% reduction in the cost of CPAP one year post-RYGB, in line with previous studies [2,32-35]. Likewise, we confirmed the possibility to stop CPAP upon clinical examination and polysomnography. In contrast with T2D, OSA improvement only becomes apparent when substantial reduction in BMI occurs, suggesting the importance of maintained weight loss. Yet, as acknowledged by studies comparing the effects of surgical versus diet-induced weight loss [36], the improvement of OSA involves numerous mechanisms other than weight loss [37].

Bariatric surgery reduces all-cause mortality, particularly death from CVD [5,21,38] and improves CVD risk factors [10]. We herein confirm the decrease in medication cost for dyslipidemia and CVD, reaching significance one and two years post-RYGB. However, these reductions were not significantly sustained on the longer term, although our patients didn't regain weight over the four years follow-up (Figure 1). Previous reports showed that although 51% and 59% of the patients could stop their hypertension or dyslipidemia medications soon post-surgery [39,40], the incidence of both diseases tends to increase again on the longer term (two and ten years) [5]. The fact that in our study drugs that were used for secondary prevention of cardiovascular events were pooled with drugs for hypertension and CVD could be another reason for the observation that reductions in drug costs for CVD did not sustain over time. Secondary prevention treatment is expected not to be discontinued, even if clinical or biological parameters improve.

By contrast, we did not observe a significant decrease in psycho-neurological treatment costs, in line with previous reports [44]. Indeed no significant change in the prevalence of antidepressant prescription was observed in a retrospective study including 439 patients before and post-RYGB [44]. Likewise, we recently demonstrated that the physical, but not the mental component of quality of life significantly improved one year after surgery [46].

While medication costs for curative use decreased, preventive medication costs increased immediately post-surgery. This can be explained by the choice of prevention regimen in our department [15]. Although the cost for preventive medication decreased over time, daily minerals and vitamins should never be discontinued as the prevention of nutrient deficiencies is lifelong [15].

Overall, the strength of our study lies in the fact that the evolution of treatment costs for obesity-related diseases was confronted with clinical examination and biological parameters obtained at each follow-up time point. This highlights the need for frequent medical follow-up enabling healthcare professionals to adapt the treatment to patients' needs in order to avoid side effects, such as hypoglycemia with antidiabetic drugs. Furthermore, these patients should receive sufficient information about their medication use, and need frequent adaptation of the medication scheme after surgery to provide correct adherence. We deliberately chose to limit our analysis on the impact of RYGB only, since different bariatric surgery techniques induce different results in terms of obesity-related diseases improvement or remission, thus impacting on drug associated costs.

However, our study presents some limitations. The medication classification in preventive and curative use, and the different comorbidities, is rather arbitrary. Besides, the recruitment of patients in a university hospital reflects the most severe obese patients with worse conditions which might reinforce the beneficial cost's reduction we herein observe. To

generalize our findings, our results need to be verified in a more general population of candidates to RYBG to validate whether they still hold true.

Finally, we decided to focus on treatment costs and didn't address other costs related to surgery follow-up, such as hospital days and non-primary care visits, thus we cannot conclude on the total health care costs. Some recent studies have however addressed this issue. The SOS study demonstrated that hospital days and visits were significantly reduced from 7 years and onwards after surgery when comparing surgery to non-surgery obese patients [13]. By contrast, Weiner *et al* failed to observe any difference in overall health care costs between surgery patients and a matched obese group [47]. Of note, in those two studies, multiple bariatric surgeries were assessed including techniques that are known to induce surgical reoperations such as lapband and vertical gastroplasty.

Conclusion

In this study we took into account medications prescribed for obesity-related diseases and for prevention of surgical and nutritional complications, thus reflecting everyday life post-RYGB. Our study shows that RYBG induces a significant reduction of total medication costs, as early as one year post RYGB, compared to baseline. Most importantly, the reduced medication cost was maintained over time several years post-RYGB and appears mainly to be due to the significant improvement of T2D and OSA. Hence, RYGB entails economic benefits by reducing the costs and need for medication and medical devices.

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Figure legends

Figure 1: Mean BMI ± SD before and after RYGB. On the x-axis the number of patients at each time point of the follow-up is represented. *(before surgery is referred as preop, 1M: 1 month, 1Y: 1 year)*

Figure 2: Medication cost per month per person pre-and post-RYGB, subdivided in preventive and curative medication use; significant differences are shown in comparison with baseline costs. *(before surgery is referred as preop, 1M: 1 month, 1Y: 1 year)*

Figure 3: Mean cost per patient per month for the different comorbidities, among the patients who suffer from the comorbidity. *(before surgery is referred as preop, 1M: 1 month, 1Y: 1 year)*

Table legends

Table 1: Characteristics of the study cohort at baseline before RYGB surgery

Table 2: Medication cost per month (at each time point post RYGB compared to baseline)

Table 3: The different treatments for T2D before and after RYGB along the follow-up

468 **Table 1:** Characteristics of the study cohort at baseline before RYGB surgery

Patients characteristics	
Total	143
Female, n (%)	112 (78.3%)
Age (y), mean ± SD	42.9 ± 12
BMI (kg/m²), mean ± SD	48.6 ± 8.8
Obesity related diseases n (%)	
Type 2 diabetes	49 (34%)
Obstructive sleep apnea	47 (33%)
Cardiovascular disease	71 (50%)
Dyslipidemia	38 (27%)
Psycho- and neurological disorders	44 (31%)

469

Table 2: Medication cost per month (at each time point post RYGB compared to baseline)

Comorbidity	Number of patients at baseline	Average medication cost per month at baseline (€)	1 month post surgery (€)	3 months post surgery (€)	6 months post surgery (€)	1 year post surgery (€)	2 years post surgery (€)	3 years post surgery (€)	4 years post surgery (€)
Type 2 Diabetes	Patients with the comorbidity (n=49)	81.0	-52.6*** [-76.6;-28.7]	-63.3*** [-87.3;-39.4]	-66.0*** [-91.2;-40.8]	-69.2*** [-94.7;-43.7]	-67.4*** [-95.1;-39.6]	-75.35*** [-107.6;-43.1]	-81.0*** [-131.0;-31.1]
	All patients (n=143)	28.3	-20.2*** [-37.2;-3.2]	-23.3*** [-40.1;-6.6]	-24.2*** [-41.6;-6.9]	-24.9*** [-43.0;-6.8]	-24.48*** [-43.55;-5.4]	-26.7*** [-49.3;-4.1]	-28.3** [-57.2;0.55]
Obstructive sleep apnea	Patients with the comorbidity (n=47)	115.7	-14.1 [-36.9;8.7]	-21.5** [-44.3;1.3]	-50.8*** [-73.9;-27.7]	-72.7*** [-96.6;-48.8]	-91.8*** [-117.2;-66.3]	-102.8*** [-132.6;-73.1]	-101.2*** [-142.1;-60.4]
	All patients (n=143)	35.6	0.6 [-16.4;17.6]	-1.8 [-18.6;14.9]	-10.7 [-28.0;6.6]	-19.2*** [-39.4;-1.1]	-26.7*** [-45.8;-7.6]	-30.8*** [-53.4;-8.2]	-31.2*** [-60.0;-2.3]
Cardiovascular diseases	Patients with the comorbidity (n=71)	33.2	-3.9 [-23.0;15.2]	-9.4 [-28.5-9.7]	-7.4 [-27.0;12.1]	-13.6 [-33.6;6.4]	-17.1* [-37.7;3.4]	-12.3 [-36.4;11.8]	-5.5 [-37.6;26.6]
	All patients (n=143)	16.5	-2.7 [-19.7;14.2]	-5.9 [-22.3;11.3]	-4.0 [-21.3;13.4]	-6.2 [-24.3;11.9]	-7.4 [-26.5;11.7]	-4.3 [-26.9;18.3]	-1.6 [-30.5;27.3]
Dyslipidemia	Patients with the comorbidity (n=38)	27.1	-5.6 [-31.3;20.2]	-14.7 [-40.5;11.0]	-17.9 [-43.6;7.9]	-22.0* [-49.1;5.1]	-20.6 [-49.5;8.3]	-16.8 [-49.2;15.6]	-19.4 [-66.1;27.4]
	All patients (n=143)	7.2	-1.8 [-18.7;15.2]	-4.0 [-20.8;12.8]	-4.5 [-21.8;12.8]	-5.8 [-23.9;12.3]	-5.4 [-24.5;13.6]	-4.0 [-26.6;18.6]	-5.2 [-34.1;23.7]
Psycho- and neurological disorders	Patients with the comorbidity (n=44)	18.0	-5.0 [-28.5;18.6]	-5.3 [-28.8;18.3]	-2.3 [-26.8;22.2]	0.7 [-25.0;26.5]	-2.0 [-29.4;25.3]	-5.9 [-36.9;25.2]	7.7 [-29.6;44.9]
	All patients (n=143)	5.5	-1.5 [-18.4;15.5]	-1.2 [-18.0;15.6]	0.5 [-16.8;17.8]	1.6 [-16.5;19.7]	0.4 [-18.7;19.5]	-1.0 [-23.6;21.6]	5.3 [-23.6;34.2]
Total curative cost	All patients (n=143)	118.2	-42.8*** [-59.8;-25.9]	-53.3*** [-70.1;-36.5]	-54.7*** [-72.0;-37.4]	-64.9*** [-83.0;-46.8]	-74.8*** [-93.9;-55.7]	-75.0*** [-97.6;-52.4]	-68.9*** [-97.8;-40.0]

The mean difference between the medication cost per month (at each time post RYGB point compared to baseline) and the preoperative cost per month with the 95% confidence interval.
The total number of patients was 143.
*p<0.05; ** p<0.01; *** p<0.001

Table 3: The different treatments for T2D before and after RYGB along the follow-up

Therapy	Baseline	1M	3M	6M	1Y	2Y	3Y	4Y
Monotherapy (n) (oral antidiabetic (OAD)	15 (31%)	7 (33%)	7 (37%)	5 (38.5%)	3 (30%)	3 (43%)	2 (67%)	0
Bitherapy (oral antidiabetic)	10 (20%)	0	2 (10%)	2 (15.5%)	3 (30%)	2 (28.5%)	1 (33%)	0
Tritherapy (oral antidiabetic)	1 (2%)	0	0	0	0	0	0	0
OAD + insulin	20 (41%)	4 (19%)	4 (21%)	3 (23%)	3 (30%)	2 (28.5%)	0	0
Insulin only	3 (6%)	10 (48%)	6 (32%)	3 (23%)	1 (10%)	0	0	0

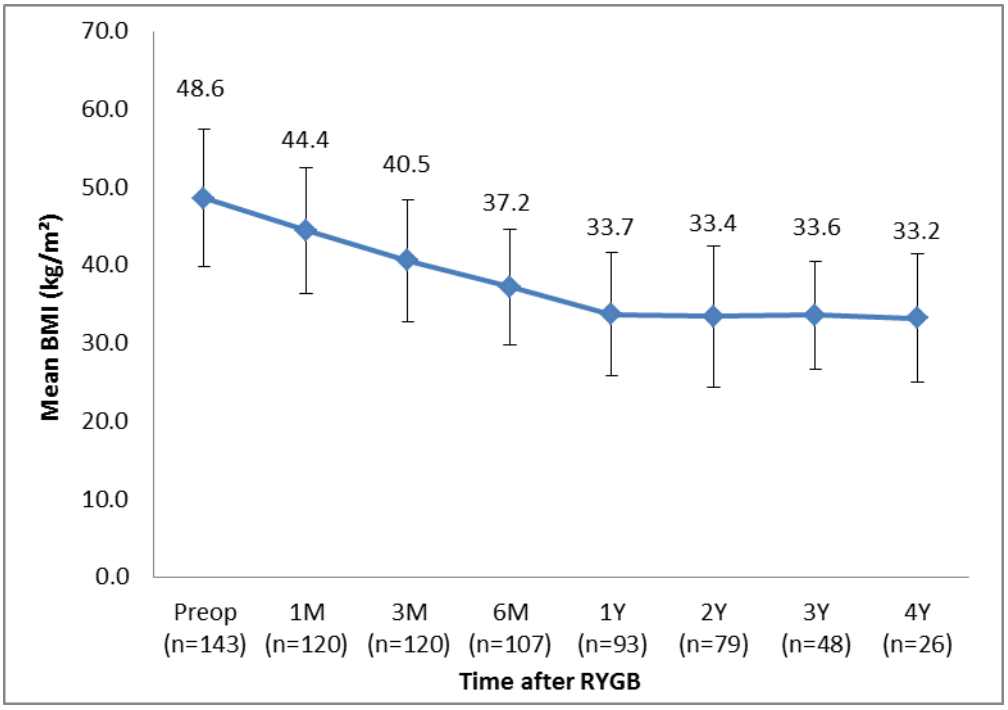

Figure 1: Mean BMI ± SD before and after RYGB. On the X axis is represented the number of patient at each time point of the follow-up. *(before surgery is referred as preop, 1M: 1 month, 1Y : 1 year)*

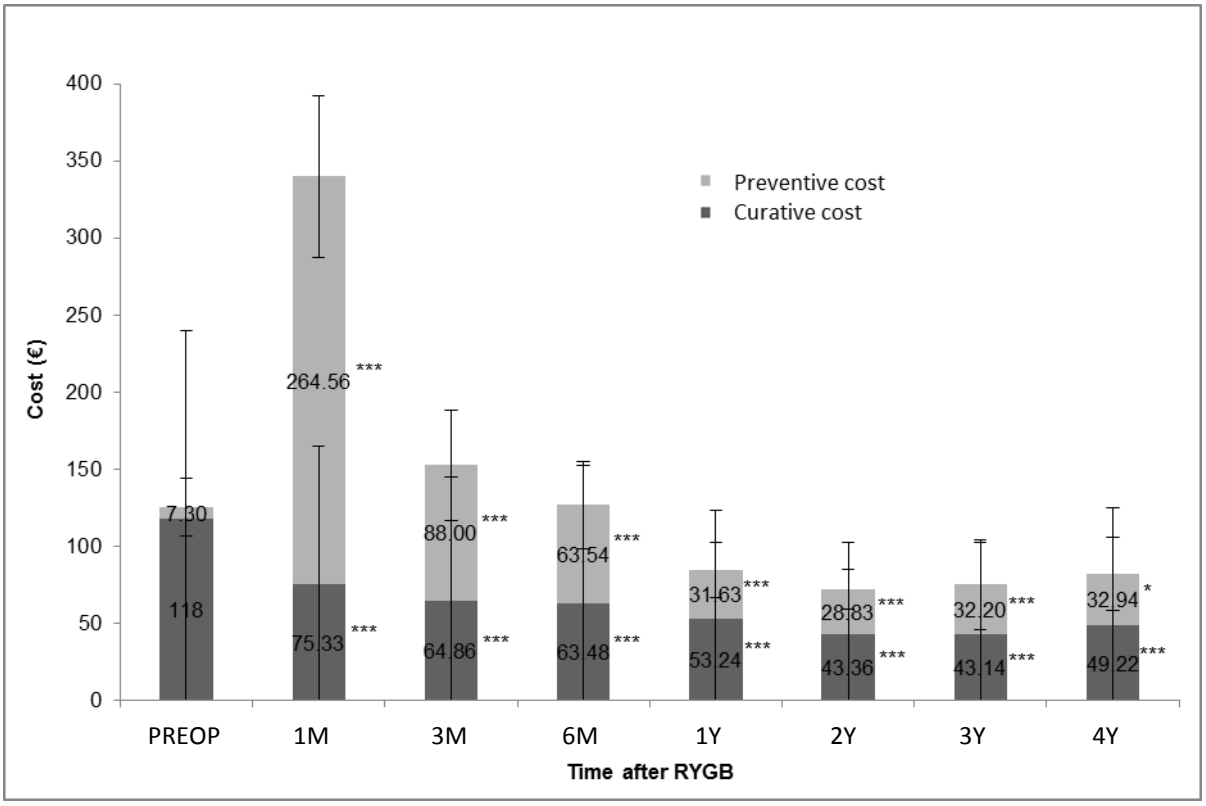

Figure 2: Medication cost per month per person pre-and post-RYGB, subdivided in preventive and curative medication use; significant differences are shown in comparison with baseline costs. *(before surgery is referred as preop, 1M: 1 month, 1Y : 1 year),* *: p<0.05; ***: *p*<0.001

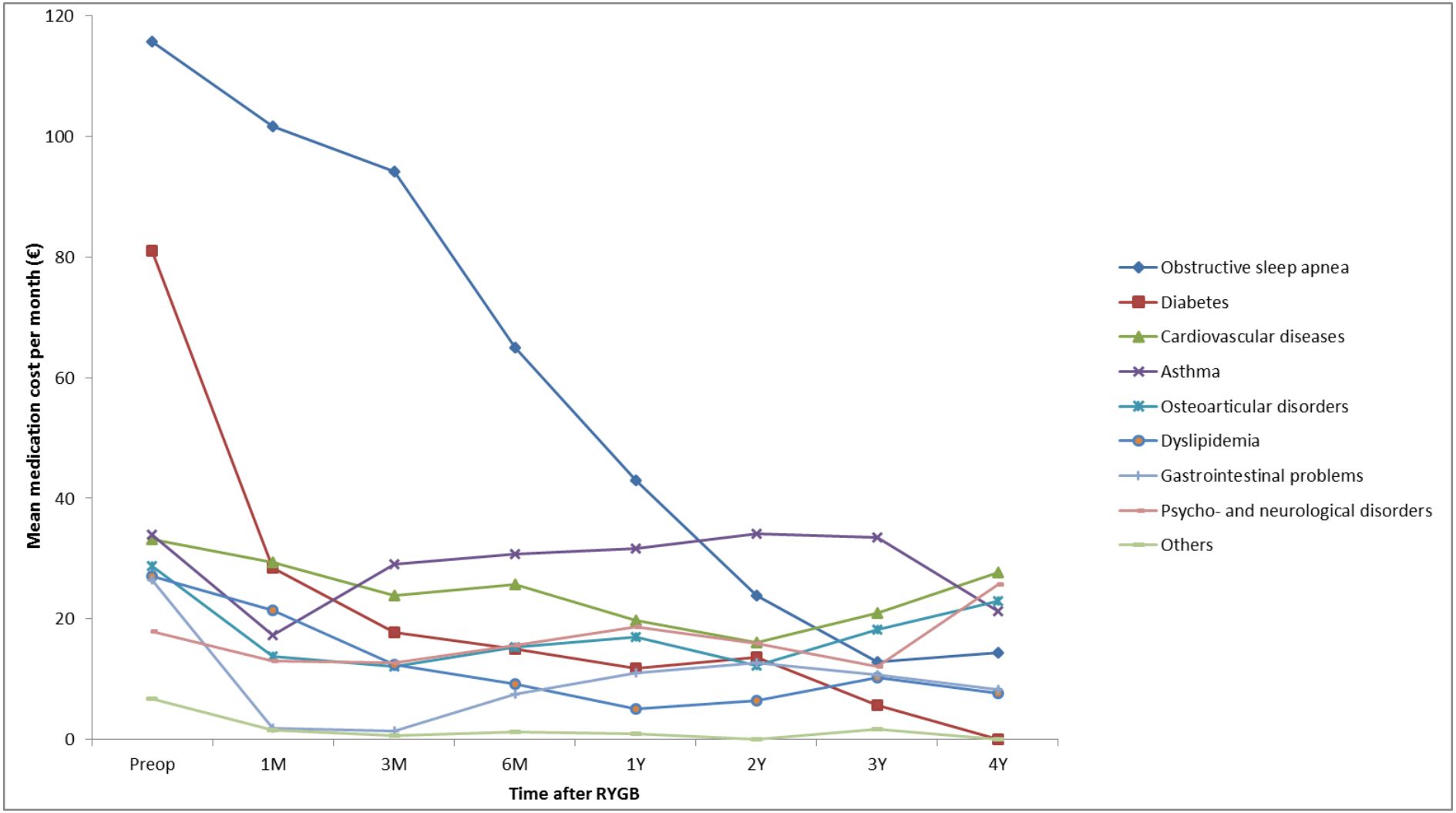

Figure 3: Mean cost per patient per month for the different comorbidities, among the patients who suffer from the comorbidity. *(before surgery is referred as preop, 1M: 1 month, 1Y : 1 year)*