

The Different Association between Metformin and Sulfonylurea Derivatives and the Risk of Cancer May be Confounded by Body Mass Index

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Abstract

Aim: Several studies in large databases suggest that in comparison to glucose-lowering sulfonylurea derivatives, metformin is associated with a reduced risk of cancer in patients with diabetes. As many databases miss relevant confounder data, our objective was to investigate whether the determinants age, body mass index (BMI), alcohol consumption, and renal function were associated with dispensing of either metformin or sulfonylurea derivatives as first drug therapy for type 2 diabetes mellitus while taking into account calendar time.

Methods: We identified 639 incident metformin users and 934 incident sulfonylurea derivatives users in the Rotterdam Study, a prospective population-based cohort study. Associations were studied using logistic regression analyses.

Results: After adjustment for all other determinants, starters with metformin had a statistically significantly higher BMI than starters with sulfonylurea derivatives (OR 1.19, 95% CI 1.04 – 1.37 for starters < July 1st 2000; OR 1.23, 95% CI 1.04 – 1.45 for starters ≥ July 1st 2000). Age, renal function, and alcohol consumption were not statistically significantly associated with the probability of dispensing metformin versus sulfonylurea derivative therapy as first drug therapy for type 2 diabetes mellitus.

Conclusion: BMI is associated with a higher probability of dispensing of metformin as first drug therapy for type 2 diabetes mellitus in comparison to sulfonylurea derivatives. BMI is associated with the risk of cancer as well as the risk of type 2 diabetes mellitus. Therefore, in studies analyzing the association between the use of metformin or sulfonylurea derivatives and the risk of cancer, BMI should be considered as an essential co-variable.

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Introduction

Type 2 diabetes mellitus is a common disorder of which the prevalence rises, due to factors such as ageing of the population and an increased number of people with overweight^[1]. Type 2 diabetes mellitus has been associated with an increased risk of several types of cancer^[2,3]. One of the most important risk factors for both diseases is an increased body mass index (BMI). It is generally known that overweight is associated with an increased risk of type 2 diabetes mellitus^[3]. Moreover, overweight has been associated with an increased risk of many cancer types^[4]. Part of this effect could be explained by an increased cancer risk in patients with diabetes through insulin resistance because high insulin levels may have a growth promoting activity^[5]. However, there is evidence that overweight is also associated with cancer through underlying mechanisms that are independent of insulin resistance^[4].

Drugs used for the treatment of type 2 diabetes mellitus might also be involved in the risk of developing cancer. In recent years, many studies have been focusing on the association between commonly prescribed drugs in type 2 diabetes mellitus and the risk of cancer^[6]. Previous studies suggested a protective effect of metformin on cancer risk, while sulfonylurea derivatives and exogenous insulin were associated with a potentially increased cancer risk^[3,6,7]. However, the association between these drugs and the risk of cancer is complex since many factors are involved, and these factors might also interfere with each other. For example, sulfonylurea derivatives can lead to weight gain, overweight is associated with insulin resistance and type 2 diabetes mellitus, and overweight as well as type 2 diabetes mellitus as well as drugs used for type 2 diabetes mellitus are associated with cancer risk^[2,8].

The most frequently prescribed oral glucose lowering drugs are metformin and sulfonylurea derivatives. Large studies published in the late nineties indicated metformin as first choice drug for type 2 diabetes mellitus^[9-11]. In these studies, the efficacy of metformin and sulfonylurea derivatives in lowering glycosylated haemoglobin (HbA1c) was equal. However, metformin therapy decreased the risk of any diabetes-related clinical endpoint, and was associated with less weight gain and less hypoglycaemic events in comparison to sulfonylurea derivatives. Since then, metformin is favoured over sulfonylurea derivatives, especially in obese patients. However, metformin is contra-indicated in those with loss of renal function with a creatinine clearance of less than 30 ml/min. Therefore, physicians prescribe metformin and sulfonylurea derivatives to different patients.

In studies on the association between the use of metformin and cancer risk in comparison to the use of sulfonylurea derivatives, it is important to adjust for a potential difference in underlying factors that determine the choice of therapy (e.g. metformin or sulfonylurea derivative). In the current study, our objective was to investigate whether the determinants age, BMI, alcohol consumption and renal function were associated with the probability of being dispensed metformin or sulfonylurea derivatives as first drug therapy for type 2 diabetes mellitus.

Methods

Setting

This study was embedded in the Rotterdam Study, a prospective population-based cohort study of chronic diseases in

the elderly population. All persons aged 55 years and over in the Ommoord district of Rotterdam, the Netherlands, were invited to participate (n = 10,275). Of them, 7,983 (78%) were enrolled between 1990 and 1993 to form the initial cohort (RS-I). The Medical Ethical Committee of the Erasmus Medical Center, Rotterdam, approved the study, and all participants gave informed consent. Participants have been continuously followed since then during follow-up rounds (1993-1995, 1997-1999, 2002-2004, 2009-2012). Furthermore, in 2000, an extended cohort was enrolled, the Rotterdam Study II (RS-II). 3,011 inhabitants entered the study and have been continuously followed since then. Detailed information on design, objectives and methods of this study have been described before^[12,13]. For both cohorts, medication dispensing data were obtained from all seven fully computerized pharmacies in the Ommoord suburb. Information on all filled prescriptions from January 1st 1991 until February 1st 2012 were available and included information on the product name of the drug, the WHO's Anatomical Therapeutic Chemical code (ATC-code), the amount dispensed, the prescribed dosage regimen and the date of dispensing.

Study population

The study population consisted of all participants in the first and second cohort of the Rotterdam study (RS-I and RS-II) with a prescription for metformin or a sulfonylurea derivative between January 1st 1991 and December 1st 2011. Use of sulfonylurea derivatives or metformin was defined as a prescription of a drug from ATC-code 'A10'^[14]. Available glucose-lowering drugs in ATC-codes 'A10BA' and 'A10BB' in the Rotterdam Study were metformin (A10BA02), glibenclamide (A10BB01), tolbutamide (A10BB03), glipizide (A10BB07), gliclazide (A10BB09), and glimepiride (A10BB12). Patients with a prescription for other glucose-lowering medication prior to the start of metformin or sulfonylurea derivative therapy were excluded. To ensure that all participants were incident users, a prescription free period of 90 days was obligatory and all metformin and sulfonylurea derivatives users with a first prescription before April 1st 1991 were excluded.

Outcome and covariables

The outcome of interest was starting with metformin or with a sulfonylurea derivative as first choice treatment of type 2 diabetes mellitus.

The determinants BMI and renal function were considered as factors influencing the choice for metformin *versus* sulfonylurea derivatives. Metformin use is associated with less weight gain and therefore it is likely that overweight subjects preferably start with metformin. Renal dysfunction (creatinine clearance < 30 ml/min) is a contraindication for metformin therapy, and therefore patients initiating metformin are expected to have a better renal function than patients initiating sulfonylurea derivative therapy. Furthermore, we considered age and alcohol consumption in the analysis. Since metformin is first choice therapy in type 2 diabetes mellitus, the large studies in the late nineties, patients initiating metformin are expected to be relatively younger than patients initiating sulfonylurea derivatives. Excessive alcohol consumption is a contraindication for the use of metformin. Since the guidelines for treatment of type 2 diabetes mellitus have changed over time, we adjusted the analysis for calendar time.

In the Rotterdam Study, during the center visits anthropometric measures were performed by well-trained nurses. BMI was calculated as weight (kg) divided by length (m²). Information on alcohol consumption was obtained by an interview at home, and was expressed in number of alcohol consumptions per day. Serum creatinine was assessed by a nonkinetic alkaline picrate (Jaffe) method^[15]. Creatinine clearance, as measure of renal function, was computed with the Cockcroft- Gault equation^[16] corrected with a factor 0.9 and standardized for 1.73 m² body surface area using the Dubois formula^[17]: $GFR = (140 - \text{age}[\text{years}]) (\text{weight}[\text{kg}] \times 1.23) (0.85 \text{ if female}) (\text{serum creatinine } [\mu\text{mol/L}]^{-1} (0.9) (1.73) (\text{weight}[\text{kg}]^{-0.425} (\text{height}[\text{cm}]^{-0.725} (0.007184)^{-1})$. Creatinine clearance generally exceeds GFR by 10% to 15% because of additional urinary creatinine excretion attributable to tubular secretion^[18]. The Cockcroft-Gault estimate of GFR was therefore additionally corrected with a factor of 0.9. When participants received a first dispensing of metformin or sulfonylurea derivative, the most recent values of the determinants were retrieved and considered in the analysis.

Statistical analysis

Differences in baseline characteristics between incident metformin users and incident sulfonylurea derivative users were tested for significance with a t-test for continuous variables and X²-test for binary variables.

We performed logistic regression analyses to investigate whether the determinants age, BMI, alcohol consumption, and renal function were associated with the probability of initiating therapy with either metformin versus sulfonylurea derivatives. All variables were included in the model as continuous variables.

Metformin was introduced as first choice therapy in patients with type 2 diabetes mellitus with normal renal function after the large scale metformin studies in 1998/1999. Since in response to these studies the national prescription guideline for general practitioners was changed, analyses were stratified for patients initiating therapy before July 1st 2000 and patients initiating therapy after July 1st 2000. All analyses were performed using SPSS software (SPSS Inc., version 20.0, Chicago, Illinois, USA).

Results

Baseline characteristics of the study population are shown in table 1. We identified 639 incident users of metformin as first drug therapy and 934 incident users of sulfonylurea derivative as first drug therapy for type 2 diabetes mellitus between April 1st 1991 and December 1st 2011. The median start- date for metformin therapy was approximately 9 years later (November 2006) compared to sulfonylurea derivatives (August 1997). Starters of metformin had a higher BMI ($P < .0001$), were younger ($P < .0001$), and consumed more units of alcohol per day ($P = .005$) compared to starters of sulfonylurea derivatives.

The results of the logistic regression analysis on the probability of patients with type 2 diabetes mellitus starting with metformin versus sulfonylurea derivatives are shown in table 2. Calendar time was associated with the probability of starting with metformin versus sulfonylurea derivatives (P -value $< .0001$). Results are therefore presented stratified for those starting before and after July 1st 2000. In univariate analyses, in patients that started drugs for type 2 diabetes mellitus before July 1st 2000, lower age (OR 0.95; 95%CI .92 – .98) and higher BMI (OR 1.16; 95%CI 1.03 – 1.29) were significantly associated with being dispensed metformin. Also in patients who started drugs for type 2 diabetes mellitus after July 1st 2000, lower age (OR 0.97; 95% CI .95 – .99) and higher BMI (OR 1.20; 95% CI 1.13 – 1.27) were significantly associated with being dispensed metformin. For time frames, renal function nor alcohol consumption were associated with dispensing of metformin.

After further adjustment for the other potential confounders, only BMI was statistically significantly associated with the probability of dispensing metformin versus sulfonylurea derivatives as first prescription independently of calendar time (table 2). Starters before July 1st 2000 showed an OR of 1.19 (95% CI 1.04 – 1.37) and starters after July 1st 2000 showed an OR of 1.23 (95% CI 1.04 – 1.45) for BMI. In contrast with the univariate analyses, in the multivariate model, age showed no statistically significant association with the probability of starting with metformin versus sulfonylurea derivatives. Similar to the univariate analyses, in the adjusted analyses, null results were found for alcohol consumption and renal function.

Table 1: Baseline characteristics of the study population of incident metformin and sulfonylurea derivative users.

	Starters with Metformin (N = 639)	Starters with Sulfonylurea derivatives (N = 934)	P
Age, years, mean(SD)	69.2 (10.8)	71.3 (10.7)	< .0001
Men, N(%)	288 (45.1%)	420 (45.0%)	.968
BMI, kg/m ² , mean(SD)	30.7 (5.3)	28.2 (4.0)	< .0001
Alcohol consumption, units/day, mean(SD)	1.40 (1.5)	1.16 (1.7)	.005
Renal function: GFR, ml/min, mean(SD) (min – max)	74.5 (19.0) (40.1 – 145.3)	75.8 (19.7) (20.7 – 164.6)	.732
Start date first prescription			
- Median	09 Nov 2006	21 Aug 1997	
- First start date in database	23 Aug 1991	02 Apr 1991	
- Last start date in database	23 Nov 2011	18 Nov 2011	
Starters < 1 July 2000 (N)	38	678	
Starters ≥ 1 July 2000 (N)	601	256	

SD: standard deviation; BMI: body mass index; GFR: glomerular filtration rate

Table 2: Results of the logistic regression analysis on the association between determinants and the probability of starting with metformin versus sulfonylurea derivatives – stratified on start date <1 July 2000 and start date ≥ 1 July 2000.

	Start date < 1 July 2000				Start date ≥ 1 July 2000			
	OR	β	95%CI	P	OR	β	95%CI	P
Analysis per covariate*								
• Age	0.95	-.050	.92 - .98	.001	0.97	-.030	.95 - .99	<.0001
• BMI	1.16	.144	1.03 – 1.29	.011	1.20	.180	1.13 – 1.27	<.0001
• Alcohol consumption	0.89	-.112	.70 – 1.14	.373	1.04	.040	.91 – 1.19	.556
• Renal function	0.96	-.005	.96 – 1.03	.755	0.97	-.035	.93 – 1.01	.081
Full model†								
Age	0.92	-.082	.83 – 1.02	.118	0.95	-.051	.87 – 1.04	.266
BMI	1.19	.176	1.04 – 1.37	.011	1.23	.206	1.04 – 1.45	.017
Alcohol consumption	1.26	.228	.86 – 1.78	.202	0.96	-.038	.49 – 1.89	.913
Renal function	0.98	-.019	.94 – 1.02	.374	0.95	-.048	.91 – 1.01	.066

*Model with covariate separately in the model, adjusted for calendar time. †Full model with all covariates including calendar time in the model. OR: odds ratio; β: beta; CI: confidence interval; BMI: body mass index. Bold values indicate statistically significant associations.

Discussion

In this population-based study, BMI was statistically significantly associated with an increased probability of dispensing of metformin as first drug therapy for type 2 diabetes mellitus. Patients starting on metformin therapy have a significantly higher BMI than patients starting on sulfonylurea derivatives.

This study demonstrates the importance of BMI in the choice of first therapy for type 2 diabetes mellitus. With regard to calendar time, the association between BMI and the probability of getting metformin versus sulfonylurea derivatives as first prescription was somewhat stronger in patients initiating therapy after July 1st 2000 than in patients initiating therapy before July 1st 2000. This is expected, since large studies in the late nineties indicated metformin as first choice therapy in type 2 diabetes mellitus patients, amongst others because of less weight gain with the use of metformin^[9-11]. Before these studies, sulfonylurea derivatives were more often prescribed. In continuation of these studies the prescription guidelines for physicians were adapted, leading to metformin as first line therapy for type 2 diabetes mellitus, especially in those with overweight. Based on the contra-indication, one would also expect renal function to be an important determinant in the choice of therapy. However, in this study we could not demonstrate this. The mean renal function in the Rotterdam Study was about 75 ml/min, while according to the Dutch prescription guidelines metformin is contraindicated in patient with a GFR < 30 ml/min. Therefore, the majority of the population would not have a contra-indication for metformin (N = 4 participants with a GFR < 30 ml/min). However, renal function is not measured at every Rotterdam Study visit, and especially in the metformin group data on renal function was missing. This might also explain why we did not find an association between renal function and the probability of dispensing of metformin as initial therapy. As expected, metformin users were relatively younger, but age itself was not a statistically significant determinant in the choice of therapy after adjustment for other determinants.

Increased BMI is associated with an increased risk of type 2 diabetes mellitus as well as an increased risk of cancer^[3,4]. However, this study showed that BMI is also associated with the

probability of being dispensed metformin versus sulfonylurea derivatives. Therefore, when analyses are performed assessing the association between the use of these drugs and the risk of cancer, BMI should be considered as a confounder. Previous studies investigating the association between drugs used in type 2 diabetes mellitus and cancer risk suggested a protective effect of metformin on cancer risk, while sulfonylurea derivatives and exogenous insulin were associated with a potentially increased cancer risk^[3,6,7]. However, possible biological mechanisms explaining these associations are largely speculative and more research is needed to elucidate the true magnitude and direction of these associations. For example, the decreased risk of cancer in those using metformin compared with those using sulfonylurea derivatives could also be explained as an increased risk of cancer in users of sulfonylurea derivatives compared with users of metformin^[19]. Moreover, although several studies on this topic adjusted for BMI or match on BMI^[20-28], there are also several studies that do not consider BMI as confounder^[19,29-32]. The question remains whether in these studies lacking BMI adjustment and demonstrating a protective effect of metformin on cancer risk^[19,29-32], indeed the protective effect persists when these studies adjust for BMI. In our study, metformin users had a higher BMI than sulfonylurea derivatives users, which makes metformin users hypothetically potentially more at risk for cancer than sulfonylurea derivative users with regard to BMI as risk factor. When studies demonstrated a protective effect on cancer risk for metformin users compared to sulfonylurea derivatives users without BMI adjustment, this protective effect might therefore change when BMI is considered as a confounder.

As discussed, the association between drugs used in type 2 diabetes mellitus, and the risk of cancer is complex and investigating this association requires accurate analysis methods to prevent biased results. Underlying mutual risk factors are involved and considering these factors as potential confounders or effect modifiers is obligatory. Furthermore, studies performing these kind of analyses are susceptible for ‘reverse causation’ where an undetected cancer causes changes in glucose and insulin metabolism leading to the onset of diabetes, and for ‘detection bias’ where cancer is more likely to be diagnosed in newly diagnosed patients with diabetes since they are more frequently

contacting a physician. Last, 'depletion of susceptibles' should be considered where patients with diabetes already died of other causes and are less susceptible of being diagnosed with cancer^[7,33]. Taking into account all these factors is of major importance and interest in future studies investigating the association between drugs used in type 2 diabetes mellitus and cancer risk, and will hopefully elucidate more insights in the true association. Given the results of the current study, we can add that these future studies should be adjusted for BMI.

However, limitations of the current study should be considered. Cohort studies are prone to selection bias, information bias and confounding. The risk of selection or information bias is unlikely since the Rotterdam Study is a population-based cohort study, in which data is collected prospectively without prior knowledge of the aim of this study. In the analysis, we adjusted for calendar time. In the Rotterdam Study, participants are visiting the center at every 4 - 5 years of follow-up period and new data are collected. We considered the measurements of for example BMI and alcohol consumption which were the closest to the initial dispensing date. Unfortunately, we had missing data on renal function. Another limitation is that we were not able to filter out those who used metformin for other indications (e.g. polycystic ovarian disease). However, such diseases occur at a low frequency, and these indications are not registered in the Netherlands. Consequently, the number of those using metformin for indications other than diabetes most likely was too low to bias the risk estimates in our study.

Conclusion

In conclusion, BMI is associated with a higher probability of dispensing of metformin as first drug therapy for type 2 diabetes mellitus in comparison to sulfonylurea derivatives. Since BMI is associated with the risk of cancer as well as the risk of type 2 diabetes mellitus, studies analyzing the association between the use of metformin or sulfonylurea derivatives and the risk of cancer should also consider BMI as determinant in the analyses.

Implications

With rising prevalence of type 2 diabetes mellitus, health care educators/providers should also be aware of the long term complications of diabetes mellitus such as an increased risk of several types of cancer. BMI has been associated with an increased risk of type 2 diabetes mellitus as well as an increased cancer risk. Furthermore, studies have suggested a protective effect of metformin on cancer risk, while sulfonylurea derivatives and exogenous insulin were associated with a potentially increased cancer risk. Health care educators/providers should be aware of the complexity of these associations since all these factors may contribute differently to the risk of development of, for example, the diagnosis of cancer.

Data from this study demonstrate that BMI is an essential covariable in studies analyzing the association between the use of metformin or sulfonylurea derivatives and the risk of cancer. Knowledge about the correct confounders is essential to elucidate the direction of the effect of the oral glucose lowering drugs on cancer risk. Although several studies on this topic adjusted for BMI or match on BMI, there are also several studies that do not consider BMI as confounder. The question

remains whether, in these studies lacking BMI adjustment, the effect might change when BMI is considered as a confounder. Due to the complex association between BMI, type 2 diabetes mellitus, drugs used for type 2 diabetes mellitus, and cancer risk, one should always consider BMI as a co-variable.

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