A statistical analysis of the treatment of type 2 diabetes in the presence of chronic kidney disease in patients hospitalized for heart failure

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Abstract Many patients suffering chronic kidney disease are associated with a type 2 diabetes mellitus. Different therapies for the treatment of type 2 diabetes have been considered. This paper aims to check whether these therapies can be affected by the presence of the kidney disease. The study was conducted on a sample of patients who were hospitalized for heart failure in CAULE (Complejo Asistencial Universitario de León).

1 Introduction

There is an extensive recent literature involving jointly the type 2 diabetes mellitus (T2DM), the chronic kidney disease (CKD) and the heart failure (HF) as well as their medical/pharmacological treatment (see, for instance, [1]-[5], [7]-[9], [11], [12]).

The study in this paper is constrained to a sample from a subpopulation of type 2 DM patients. This subpopulation refers to the type 2 DM patients who were hospitalized for heart failure. The sample corresponded to that of 248 patients who were admitted in CAULE along a certain recent period.

The statistical analysis has aimed to get conclusions on the dependence of the treatment received by type 2 DM patients who were hospitalized for heart failure (e.g., diet, insulin, metformin, sulfonylureas, etc. or the combination of some of them) and the presence/absence of CKD. Data management and

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Pedro Gil was our uncle (López-Gil) and 'scientific grandfather' (Lubiano), and we have known each other thanks to him. Pedro was the first person helping us when we both join the University of Oviedo to start the BSc in Medicine (López-Gil) and the PhD in Math and teaching asssistance in Statistics. This first paper we are coauthoring should be dedicated to Pedro's memory.

statistical analysis were carried out using SPSS software (IBM SPSS Statistics version 24). The analysis has been mainly based on testing from contingency tables built from data in Table 1.

Of 248 type 2 DM hospitalized for heart failure patients, 104 suffered CKD, whereas 144 did not.

Table 1 Numbers of hospitalized for heart failure patients in CAULE receiving single or combined treatments for type 2 DM, and classified in accordance with the presence/absence of CKD and with the degree of CKD according to the classification with KDIGO 2012 [10] based on GFR categories (n-G2 = normal-Stage/Degree 2, Gi = Stage/Degree i)

treatment	CKD		CKD degrees			
	YES	NO	n-G2	G3	G4	G5
diet	9	26	26	6	3	0
glibenclamide	1	0	0	1	0	0
glicazide	0	2	2	0	0	0
glimepiride	2	4	4	1	0	1
insulin	44	32	32	31	13	0
insulin + glicazide	0	1	1	0	0	0
insulin + linagliptin	3	2	2	2	1	0
insulin + metformin	5	6	6	3	2	0
insulin + metformin + lixisenatide	0	1	1	0	0	0
insulin + metformin + repaglinide	0	1	1	0	0	0
insulin + repaglinide	1	0	0	1	0	0
insulin + saxagliptin	0	1	1	0	0	0
insulin + sitagliptin	1	1	1	1	0	0
insulin + sitagliptin + metformin	3	1	1	2	1	0
insulin + vildagliptin	3	0	0	2	0	1
insulin + vildagliptin + metformin	0	3	3	0	0	0
linagliptin	6	2	2	5	1	0
linagliptin + metformin	1	0	0	0	1	0
linagliptin + metformin + repaglinide	1	0	0	1	0	0
linagliptin + repaglinide	1	0	0	1	0	0
liraglutide + metformin	0	1	1	0	0	0
metformin	4	34	34	2	2	0
metformin + glicazide	1	0	0	1	0	0
metformin + glimepiride	0	1	1	0	0	0
repaglinide	3	0	0	0	2	1
repaglinide + linagliptin + metformin	1	0	0	0	1	0
sitagliptin	3	1	1	2	1	0
sitagliptin + glimepiride	1	0	0	1	0	0
sitagliptin + metformin	1	8	8	0	1	0
sitagliptin + metformin + glibenclamide	0	1	1	0	0	0
sitagliptin + metformin + glicazide	0	1	1	0	0	0
sitagliptin + repaglinide	1	0	0	0	1	0
vildagliptin	4	2	2	3	1	0
vildagliptin + glicazide	0	1	1	0	0	0
vildagliptin + glimepiride	0	1	1	0	0	0
vildagliptin + metformin	4	10	10	3	1	0

2 Analyzing the dependence of receiving each type 2 DM treatment and the presence of CKD

This section aims to discuss whether there is a statistical dependence between receiving each of the single type 2 DM treatment and the presence of CKD. The discussion for each single treatment has been carried out on the basis of a 2×2 contingency table independence test. More concretely, whenever the Pearson chi-square test is reliable because of the cells counts being enough it has been applied; on the contrary, we have considered the exact Fisher procedure.

As an example of such contingency tables analysis, assume the selected treatment is metformin. Then, the associated contigency table is the one given in Table 2.

Table 2 2×2 contingency table of type 2 DM hospitalized for heart failure patients in CAULE where the two involved variables are receiving or not metformin treatment and suffering or not CKD)

	suffering from CKD	not suffering from CKD
with metformin treatment	21	68
without metformin treatment	83	76

The value of the Pearson chi-square statistic is equal to 19.176, whence the p-value is .000012 and hence there is a significant dependence between the metformin treatment and the presence of CKD.

Separate conclusions for each of the treatments can be found gathered in Table 3.

The obtained p-values for testing independence in the considered 2×2 contingency tables have been quite conclusive. In this way, for each of the involved treatments these p-values have been either much greater than .1 or much lower than .01 (but for the diet which is slightly lower than .05). Consequently, we can conclude that the diet treatment of type 2 DM hospitalized for heart failure patients seems to be significantly dependent on the presence of CKD, linagliptin and repaglinide treatments are quite significantly dependent and insulin and metformin treatments are very significantly dependent.

In cases the presence of CKD influences the diabetic treatment, we can consider a deeper analysis which are to be presented in the following section.

Table 3 Summary of statistical conclusions from 2×2 contingency table of type 2 DM hospitalized for heart failure patients in CAULE where the two involved variables are receiving or not the given treatment and suffering or not CKD

treatment	suffering from CKD	not suffering from CKD from CKD	differences
diet	9	26	**significant** ($p < .05$)
glibenclamide	1	1	not significant ($p = 1$)
glicazide	1	5	not significant ($p >> .1$)
glimepiride	3	6	not significant ($p >> .1$)
insulin	60	49	**significant** ($p << .01$)
linagliptin	13	4	**significant** ($p < .01$)
liraglutide	0	1	not significant ($p = 1$)
lixisenatide	0	1	not significant ($p = 1$)
metformin	21	68	**significant** ($p << .01$)
repaglinide	8	1	**significant** ($p < .01$)
saxagliptin	0	1	not significant ($p = 1$)
sitagliptin	10	13	not significant ($p >> .1$)
vildagliptin	11	17	not significant ($p >> .1$)

3 Analyzing the dependence of receiving each type 2 DM treatment and the degree of CKD

For each of the five treatments for which differences have been shown to be significant one can develop independence contingency table tests concerning the degrees of CKD [10].

However, because of the required expected (theoretical) frequencies conditions for applying contingency tests, instead of having 2×4 tables, we have reduced them by removing either G5 or both n-G2 and G5. The conclusions have been gathered in next subsections.

3.1 Diet treatment dependence on the CKD degree

In case of diet (for which the influence of the CKD was slightly significant), the Pearson chi-square test p-value equals .131.

Close p-values are obtained for the likelihood ratio and the linear-by-linear association tests. Consequently, there are not statistical evidences for the CKD degree influencing to prescribe or not diet.

Table 4 2×3 contingency table of type 2 DM hospitalized for heart failure patients in CAULE where the two involved variables are following or not a diet and degrees of CKD

	CKD degrees		
treatment	n-G2	G3	G4
diet	26	6	3
not diet	118	63	29

3.2 Insulin treatment dependence on the CKD degree

In case of insulin (for which the influence of the CKD was strongly significant), the Pearson chi-square test p-value equals .001.

Table 5 2×3 contingency table of type 2 DM hospitalized for heart failure patients in CAULE where the two involved variables are following or not insulin treatment and degrees of CKD

	CKD degrees		
treatment	n-G2	G3	G4
insulin	49	42	17
not insulin	95	27	15

Close p-values are obtained for the likelihood ratio and the linear-by-linear association tests. Consequently, as for the presence of CKD, the CKD degree significantly affects the use of insulin therapy.

3.3 Linagliptin treatment dependence on the CKD degree

In case of linagliptin (for which the influence of the CKD was quite significant), the exact Fisher test p-value equals 1, but one should take into account that only degrees G3 and G4 could be considered for the expected frequencies being right.

Close asymptotic p-values are obtained for the Pearson chi-square, the chi-square with Yates correction for continuity, the likelihood ratio, and the linear-by-linear association tests. Consequently, although the influence of the CKD was quite significant on prescribing the linagliptin treatment, there is no statistical evidences for the CKD degree influencing it.

Table 6 2×2 contingency table of type 2 DM hospitalized for heart failure patients in CAULE where the two involved variables are following or not linagliptin treatment and degrees of CKD

	CKD degrees	
treatment	G3	G4
linagliptin	9	4
not linagliptin	60	28

3.4 Metformin dependence on the CKD degree

In case of metformin (for which the influence of the CKD was strongly significant), the Pearson chi-square test p-value is lower than .0001.

Table 7 2×3 contingency table of type 2 DM hospitalized for heart failure patients in CAULE where the two involved variables are following or not metformin treatment and degrees of CKD

	CKD degrees		
treatment	n-G2	G3	G4
metformin	68	12	9
not metformin	76	57	23

Close p-values are obtained for the likelihood ratio and the linear-by-linear association tests. Consequently, as for the presence of CKD, the CKD degree significantly affects the use of metformin therapy.

3.5 Repaglinide treatment dependence on the CKD degree

Finally, in case of repaglinide (for which the influence of the CKD was quite significant), the exact Fisher test p-value equals .204, and only degrees G3 and G4 could be considered for the expected frequencies accomplishing the required conditions.

Close asymptotic p-values are obtained for the Pearson chi-square, the chi-square with Yates correction for continuity, the likelihood ratio, and the linear-by-linear association tests. Consequently, although the influence of the CKD was quite significant on prescribing the ripaglidine treatment, there is no statistical evidences for the CKD degree influencing it.

Table 8 2×2 contingency table of type 2 DM hospitalized for heart failure patients in CAULE where the two involved variables are following or not repaglinide treatment and degrees of CKD

	CKD degrees	
treatment	G3	G4
repaglinide	3	4
not repaglinide	66	28

4 Concluding remarks

From the performed contingency tables-based statistical analysis it is quite clear that CKD presence and degrees significantly influence the farmacological treatment of type 2 DM hospitalized for heart failure in case of insulin and metmorfin. For rest of treatments, differences have not been shown to be significant.

By looking at data in Table 1, it is clear that the most usual farmacological treatment for CDK patients is insulin, whereas metformin is the most commonly employed for non-CKD. Consequently, taking into account the current Clinical Practice Guidelines (see, e.g, [6, 13]), the adequate treatment of type 2 DM in patients with CKD requires a thorough knowledge of their pharmacokinecits by all professionals involved in the treatments and, first of all, a good coordination between primary care physicians and specialists to provide a multifaceted care program to reduce progression of disease.

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