Prescribing of Non-Steroidal Anti-Inflammatory Drugs to Patients with Diabetes Mellitus in Portugal

Prescrição de Anti-Inflamatórios Não Esteroides a Doentes com Diabetes *Mellitus* em Portugal

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ABSTRACT

Introduction: Portugal presents the highest incidence of stage 5 chronic kidney disease in Europe. It is speculated that a high consumption of non-steroidal anti-inflammatory drugs may contribute to this high incidence. Our aim was to characterize the prescription of non-steroidal anti-inflammatory drugs to patients with diabetes mellitus in Portugal.

Material and Methods: We analyzed the national prescription database in triennium 2015 - 2017. In patients with diabetes mellitus, we evaluated the prescription of non-steroidal anti-inflammatory drugs according to age, gender and region of the patient and specialty of the prescribing physician. We evaluated the prescription of non-steroidal anti-inflammatory drugs in all patients with diabetes mellitus, in patients with presumed renal impairment, and in those with concomitant prescription of angiotensin converting enzyme inhibitors or angiotensin receptor antagonists.

Results: We analyzed 23,320,620 prescriptions, corresponding to 610,157 adults, including 104,306 patients with diabetes mellitus. The most prescribed non-steroidal anti-inflammatory drugs were ibuprofen (20.1%), metamizole (14.7%), and diclofenac (11.4%). The prescription of non-steroidal anti-inflammatory drugs was higher in females, in patients aged 51 - 70 years and in the Alentejo region. Non-steroidal anti-inflammatory drugs were prescribed to 70.6% of patients with diabetes mellitus, from which 10.6% were prescribed ≥ 10 packages during the three years. Among patients with diabetes mellitus on angiotensin converting enzyme inhibitors/angiotensin receptor antagonists and with presumed reduction in kidney function, 69.3% were prescribed non-steroidal anti-inflammatory drugs and 11.5% were prescribed ≥ 10 packages during the three years.

Discussion: The level of prescribing of non-steroidal anti-inflammatory drugs to patients with diabetes mellitus is high. The concern of reducing non-steroidal anti-inflammatory drugs prescription to patients already on angiotensin converting enzyme inhibitors/angiotensin receptor antagonists and/or decreased renal function does not seem to exist.

Conclusion: In Portugal, the level of prescribing of non-steroidal anti-inflammatory drugs to patients with diabetes mellitus should be reduced, particularly in the subgroups identified with higher prescription and with higher risk of progression to stage 5 chronic kidney disease.

Keywords: Angiotensin-Converting Enzyme Inhibitors; Angiotensin Receptor Antagonists; Anti-Inflammatory Agents, Non-Steroidal; Diabetes Mellitus; Renal Insufficiency, Chronic

RESUMO

Introdução: Portugal apresenta a incidência mais elevada de doença renal crónica estádio 5 na Europa. Especula-se que o elevado consumo de anti-inflamatórios não esteroides possa contribuir para esta incidência. O objetivo do presente estudo foi caracterizar a prescrição de anti-inflamatórios não esteroides a doentes com diabetes *mellitus* em Portugal.

Material e Métodos: Na Base de Dados Nacional de Prescrições do Ministério da Saúde, triénio 2015 - 2017, analisámos a prescrição de anti-inflamatórios não esteroides em doentes com diabetes *mellitus*, de acordo com a idade, género e região do doente e a especialidade do médico prescritor. Avaliámos a prescrição de anti-inflamatórios não esteroides no total de doentes com diabetes *mellitus*, em doentes com diminuição presumida da função renal e naqueles com prescrição concomitante de inibidores da enzima de conversão da angiotensina ou antagonistas dos recetores da angiotensina.

Resultados: Analisámos 23 320 620 prescrições, correspondendo a 610 157 adultos, dos quais 104 306 doentes com diabetes *mellitus*. Os anti-inflamatórios não esteroides mais prescritos foram ibuprofeno (20,1%), metamizol (14,7%) e diclofenac (11,4%). A prescrição foi mais frequente nas mulheres, nos doentes com 51 - 70 anos e no Alentejo. Foram prescritos anti-inflamatórios não esteroides a 70,6% dos doentes com diabetes *mellitus*, dos quais 10,6% receberam prescrições de ≥ 10 embalagens durante os três anos. Dos doentes com diabetes *mellitus* medicados com inibidores da enzima de conversão da angiotensina ou antagonistas dos receptores da angiotensina e com diminuição presumida da taxa de filtração glomerular, 69,3% receberam prescrição de anti-inflamatórios não esteroides e 11,5% receberam ≥ 10 embalagens durante os três anos.

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Discussão: A prescrição de anti-inflamatórios não esteroides na diabetes *mellitus* é elevada. Não parece existir uma preocupação na menor utilização de anti-inflamatórios não esteroides em doentes simultaneamente medicados com inibidores da enzima de conversão da angiotensina ou antagonistas dos recetores da angiotensina e/ou com diminuição da função renal.
Conclusão: A prescrição de anti-inflamatórios não esteroides em Portugal a doentes com diabetes *mellitus* deverá ser reduzida, particularmente nos subgrupos identificados com prescrição mais elevada e com maior risco de progressão para doença renal crónica estádio 5.
Palavras-chave: Antagonistas de Receptores de Angiotensina; Anti-Inflamatórios não Esteroides; Diabetes Mellitus; Inibidores da Enzima Conversora de Angiotensina; Insuficiência Renal Crónica

INTRODUCTION

Portugal Portugal shows the highest incidence of end-stage renal disease [stage 5 of chronic kidney disease (CKD)] and the need for renal replacement therapy in Europe.[1,2] An increasing prevalence of diabetes mellitus and hypertension, increasing mean life expectancy with subsequent population ageing, improved healthcare with an increasing survival of patients with CKD-related cardiovascular and cancer chronic pathologies, in addition to an increasing acceptance and access to renal replacement therapy in Portugal have been suggested by some studies as some of the major contributions to this reality.[3]

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most widely used therapeutic group, with analgesic, anti-inflammatory and antipyretic actions.[4] There is an increasing risk of decline in renal function with the use of NSAIDs in patients treated with angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin II receptor blockers (ARBs) as both drug classes contribute to glomerular filtration rate (GFR) decline.[5,6] For this reason, the use of NSAIDs, including cyclooxygenase-2 (COX-2) inhibitors, should be avoided in patients with CKD. Other drugs including acetaminophen, tramadol or short-term opioid analgesics have the same therapeutic efficacy and are safer than NSAIDs.[7] A frequent use of NSAIDs in general population has been found by different Portuguese studies.[8–12]

This study was aimed at analysing the prescription of NSAIDs in patients with diabetes mellitus in Portugal, particularly in patients with presumed renal impairment (GFR decline) and/or treated with ACE-I or ARBs.

MATERIAL AND METHODS

Data source

A group of patients randomly selected from the 2015 to 2017 BDNP (*Base de Dados Nacional de Prescrições*) database of the Ministry of Health was analysed, with no specific constraints. Information regarding drug prescriptions, patients and prescribing physicians are included in the BDNP, including no other patient's data, such as personal history or test results. The access to anonymised data from the BDNP was approved by the *Serviços Partilhados do Ministério da Saúde*.

Study sample

This was a retrospective study involving adult patients (aged 18 and older) diagnosed with diabetes mellitus (diagnosis was inferred by prescriptions) who were prescribed oral (metformin, sulfonylureas, DPP-4 inhibitors, nateglinide, acarbose, pioglitazone and SGLT2 inhibitors) or injectable hypoglycaemic agents (insulin or analogues) during the study period. These patients were divided into four groups: patients with diabetes mellitus not treated with ACE-I/ARBs and no presumed renal impairment (no presumed GFR decline) – A; patients with diabetes mellitus not treated with ACE-I/ARBs and with presumed renal impairment – B; patients with diabetes mellitus treated with ACE-I/ARBs and no presumed renal impairment – C; patients with diabetes mellitus treated with ACE-I/ARBs and presumed renal impairment – D. Patients who were not prescribed metformin and treated with oral hypoglycaemic agents with an indication to be used in patients with renal impairment (gliclazide, glimepiride, glipizide, nateglinide, alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin, pioglitazone) were considered as presenting with presumed renal impairment (GFR decline).[13-15]

NSAIDs prescribing patterns were assessed according to patient's characteristics (age, gender and healthcare region) and specialty of the prescribing physician, including NSAIDs characteristics, number of tablets and packages per patient. The relationship between NSAIDs category and healthcare region was also assessed.

Statistical analysis

Aggregated data were analysed. Continuous variables were presented as mean ± standard deviation or as median (interquartile range) whenever non-normal distribution was found. Categorical variables were presented as absolute number (percentage). Chi-square test and logistic regressions were used for the comparison of prescription rates. A p-value < 0.05 was considered as statistically significant. STATA 14.1 IC software has been used in data analysis.

RESULTS

A total of 23,320,620 prescriptions were analysed, corresponding to 610,157 adult patients (104,360 patients with diabetes mellitus). A mean age of 65.9 ± 14.0 years has been found in patients with diabetes mellitus (52.1% female). A percentage of 70.6% of these patients were prescribed NSAIDs throughout the study period, 40.4% of which were prescribed ≥ 3 packages and 10.6% ≥ 10 packages. A median of 60 tablets (interquartile range [IQR] 27 - 136) and 2 packages of NSAIDs were prescribed per patient (IQR 1 - 5).

NSAIDs prescribed to patients with diabetes mellitus according to patient's gender, age and healthcare region are shown in Table 1. Higher NSAIDs prescription rates have been found in female patients, in the three categories: ≥ 1

Table 1 – Number of packages of NSAIDs prescribed to patients with diabetes mellitus according to patient's gender, age and healthcare region

Variables	Patients with diabetes mellitus		
	≥ 1 package (%)	≥ 3 packages (%)	≥ 10 packages (%)
Gender			
Male	65.2	32.8	6.9
Female	75.6	47.5	14.0
Age group (years)			
18 - 30	68.0	29.9	2.8
31 - 40	73.7	38.2	6.1
41 - 50	73.7	42.1	8.7
51 - 60	74.0	43.1	10.6
61 - 70	72.6	43.0	12.0
71 - 80	70.1	40.8	11.8
> 80	71.2	32.4	8.9
Healthcare regions			
ARS Norte	70.3	39.3	9.7
ARS Centro	70.4	39.9	11.1
ARS Lisboa e Vale do Tejo	71.4	41.8	11.2
ARS Alentejo	72.9	43.1	12.6
ARS Algarve	67.9	38.6	10.6

A *p*–value < 0.001 was considered in all comparisons (chi-square test). A similar *p*–value < 0.001 was presented for the prescription of ≥ 1, ≥ 3 and ≥ 10 packages (logistic regression) in the analysis of patient's age as continuous variable. ARS: *Administração Regional de Saúde*.

package (75.6%), ≥ 3 packages (47.5%) and ≥ 10 packages (14%). The highest prescription rate of ≥ 1 package (74.0%) and ≥ 3 packages (43.1%) was found in the 51-60 age group, while the prescription of ≥ 10 packages was most frequent in patients aged 61-79. The highest prescription rate of NSAIDs in all categories was found in the Alentejo region (*Administração Regional de Saúde* (ARS) *do Alentejo*]: ≥ 1 package (72.9%), ≥ 3 packages (43.1%) and ≥ 10 packages (12.6%). Seven specialties corresponded to 89.8% of NSAIDs prescriptions to patients with diabetes mellitus (Table 2). A percentage of 66.8% of NSAIDs were prescribed by general practitioners, 8.0% by orthopaedic surgeons, 5.0% by internists, 3.3% by dentists, 3.0% by general surgeons, 2.2% by physiatrists and 1.5% by rheumatologists.

A percentage of 69.9% of the patients in group A were prescribed NSAIDs (38.3% ≥ 3 packages and 8.5% ≥ 10 packages), throughout the study period (Table 3), 66.5% of patients in group B (35.9% ≥ 3 packages and 8.8% ≥ 10 packages), 71.5% in group C (41.6% ≥ 3 packages and 11.5% ≥ 10 packages) and 69.3% in group D (40.2% ≥ 3 packages and 11.5% ≥10 packages). No significant differences were found between the four groups of patients regarding the percentage of patients who were prescribed NSAIDS.

The five more frequently prescribed NSAIDs to patients with diabetes mellitus (ibuprofen, 20.14%; metamizole, 14.73%; diclofenac, 11.42%; etoricoxib, 11.12%; naproxen, 10.75%) corresponded to 68.16% of the total prescribed NSAIDs (Table 4). Different NSAIDs prescription patterns have been found according to each Portuguese healthcare region (Table 5).

DISCUSSION

An increasing NSAIDs prescription rate in patients with diabetes mellitus has been found in a randomly selected group of patients. However, no significant differences between the four subgroups of patients have been found regarding the percentage of patients who were prescribed NSAIDs. These results have suggested no concern by prescribing physicians about lowering the use of NSAIDs in patients with diabetes mellitus treated with ACE-I/ARBs and/or presenting with renal impairment. This prescription pattern is particularly relevant considering the high incidence and prevalence of CKD in Portugal. The relevance of this study lies on the assessment of a modifiable risk factor (NSAIDs prescription pattern) in a Portuguese group of patients at high risk for CKD and CKD progression (patients with diabetes mellitus).

Previous studies with urban and rural populations of patients attending Portuguese healthcare centres have estimated that approximately 8% of the patients were chronically treated with NSAIDs.[8,9] A survey carried out with 450 pharmacy users from the Central region of Portugal has found the use of NSAIDs by 58% of the users over the past six months and showing a higher rate in older patients.[10] A survey carried out with 300 general practitioners nationwide on their perception regarding NSAIDs use has found that 38% of the patients they attended had consumed NSAIDs,

Table 2 – Prescription of NSAIDs to patients with diabetes mellitus according to the medical specialty of prescribing physicians

Specialty	(P%)*	Specialty	(P%)*	Specialty	(P%)*
Family Medicine	64.84	Endocrinology & Diabetes	0.38	Public Health	0.08
Orthopaedics	7.98	Neurology	0.35	Allergy Medicine	0.07
Internal Medicine	5.01	Vascular Surgery	0.33	Clinical Pathology	0.07
Dental Medicine	3.31	Psychiatry	0.30	Sports Medicine	0.03
General Surgery	3.00	Ophthalmology	0.26	Radiology	0.03
Rehabilitation Medicine	2.19	Renal Medicine	0.21	Pathology	0.02
Rheumatology	1.47	Plastic Surgery	0.17	Neuroradiology	0.02
Urology	0.93	Gastroenterology	0.17	Paediatric Surgery	0.01
Neurosurgery	0.67	Transfusion Medicine	0.14	Nuclear Medicine	0.01
Gynaecology/Obstetrics	0.65	Dermatology	0.13	Tropical Medicine	0.01
Otorhinolaryngology (ENT)	0.61	Paediatrics	0.13	Child and Adolescent Psychiatry	0.01
Anaesthesiology	0.52	Paediatric Cardiology	0.12	Medical Genetics	< 0.01
Occupational Medicine	0.46	Cardiothoracic Surgery	0.12	Clinical Pharmacology	< 0.01
Cardiology	0.43	Haematology	0.11	Forensic Medicine	< 0.01
Pulmonary Medicine	0.42	Radiation Oncology	0.09	Intensive Care Medicine	< 0.01
Dentistry	0.41	Maxillofacial Surgery	0.08	Others	3.18
Medical Oncology	0.39	Infectious Diseases	0.08		

(P%)*: NSAIDs prescriptions (%)

with no differences regarding the Portuguese healthcare region.[8] In 2014, four of the 100 best-selling medications in Portugal were NSAIDs.[11] A survey carried out in Portuguese pharmacies with NSAIDs users has found that the presence of osteoarticular pathologies was the main reason for the use of NSAIDs.[12] A 1993 study with patients attending Portuguese healthcare centres has found that 73% of these patients presented with multiple comorbidities, defined as the concomitant presence of two or more pathologies affecting the same patient.[16] It has been found that the presence of multiple comorbidities affecting the same patient is associated with poorer quality of life and greater constraint to follow-up and treatment.[17,18] A better access and streamline prescriptions and use of analgesic drugs is one of the major aims of the national plan for pain control.[19]

A decline in NSAIDs use has been found in other European countries, namely in Scotland, throughout a six-month period following the implementation of estimated GFR (eGFR) reporting in patient's blood test results. A decline from 18.8% to 15.5% in NSAIDs prescribing rate in patients with CKD stage 3 has been found, in addition to a decline from 15.4% to 10.7% in patients with CKD stage 4 and from 7.0% to 6.3% in patients with CKD stage. Rises in eGFR values have also been found in patients who stopped their NSAID treatment.[20] A regular use of NSAIDs has been found in approximately 70% of patients with CKD stage 1 to 4 in Poland.[20] A daily NSAID use in the month prior to the survey application was described by 5.5% of the patients with eGFR ≤ 60 ml/min/min/1.73 m^2, according to a North-American study with a representative group of patients of the civilian, non-institutionalised population.[21] A 26 to 40% rate of patients with CKD having been prescribed NSAIDs over the past year has been found in a South-African study.[22] Our findings must be correctly contextualised before comparing with studies carried out in other countries as the percentage of patients treated over a three-year period was analysed. In addition, a group of patients at high risk for worsening renal function when treated with NSAIDs,

Table 3 – Number of packages of NSAIDs prescribed to patients with diabetes mellitus, according to simultaneous prescription of ACE-I/ARBs and presumed renal impairment (GFR decline)

Number of packages of NSAIDs	Total of patients (n = 104,306)	A – Patients not treated with ACE-I/ARBs and with no presumed renal impairment (n = 25,307)	B - Patients not treated with ACE-I/ARBs and presumed renal impairment (n = 3,821)	C - Patients treated with ACE-I/ARBs and no presumed renal impairment (n = 61,343)	D - Patients treated with ACE-I/ARBs and presumed renal impairment (n = 13,835)
≥ 1	73,645 (70.6%)	17,678 (69.9%)	2,542 (66.5%)	43,840 (71.5%)	9,585 (69.3%)
≥ 3	42,168 (40.4%)	9,703 (38.3%)	1,373 (35.9%)	25,529 (41.6%)	5,563 (40.2%)
≥ 10	12,096 (10.6%)	2,138 (8.5%)	335 (8.8%)	7,038 (11.5%)	1,585 (11.5%)

NSAIDs: non-steroidal anti-inflammatory drugs; ARBs: angiotensin II receptor blockers; ACE-I: angiotensin-converting enzyme inhibitors; GFR: glomerular filtration rate. Adjusted *p*–values to age and gender (logistic regression) for the comparison between the groups of prescription of: ≥ 1 package 0.463 (A *vs.* B), 0.074 (C *vs.* D); ≥ 3 packages 0.323 (A *vs.* B). 0.648 (C *vs.* D); ≥ 10 packages 0.801 (A *vs.* B), 0.530 (C *vs.* D).

Table 4 – Categories and number of packages of NSAIDs prescribed to patients with diabetes mellitus

NSAIDs	Number of packages	
	n	%
Ibuprofen	77,142	20.14
Metamizole	56,426	14.73
Diclofenac	43,738	11.42
Etoricoxib	42,582	11.12
Naproxen	41,163	10.75
Nimesulide	26,623	6.95
Etodolac	21,524	5.62
Ketoprofen	12,149	3.17
Aceclofenac	11,266	2.94
Celecoxib	8,570	2.24
Acemetacin	8,080	2.11
Meloxicam	6,261	1.63
Diclofenac + Misoprostol	5,764	1.51
Piroxicam	4,995	1.30
Naproxen + Esomeprazole	4,105	1.07
Indomethacin	3,214	0.84
Lornoxicam	2,386	0.62
Dexibuprofen	2,115	0.55
Proglumetacin	1,806	0.47
Etofenamate	1,387	0.36
Others	1,684	0.46
Total	382,980	100.00

NSAIDs: non-steroidal anti-inflammatory drugs

patients with diabetes mellitus and particularly those with renal impairment (GFR decline) have been included in the study.

The therapeutic effect of NSAIDs is obtained by the inhibition of prostaglandin synthesis, with cyclo-oxygenase enzymes, from arachidonic acid.[23] Vasodilation of the afferent arteriole is stimulated by renal secretion of prostaglandins in the presence of vasoconstrictor agents such as angiotensin II and therefore with a counter-regulatory effect on vasoconstriction that is predominant in hypovolaemia situations. Patients with an effective decline in circulating volume present at high risk for the development of renal vasoconstriction and GFR decline when prostaglandin synthesis is pharmacologically inhibited. CKD is a prostaglandin-dependent physiopathological status and therefore patients with CKD are at high risk for NSAIDs-associated renal injury. It is estimated that exposure to NSAIDs doubles the risk of hospitalisation due to acute renal injury in patients with CKD. There are also idiosyncratic effects, mainly including the presence of acute interstitial nephritis and glomerular disorders, more frequently minimal-change disease and less frequently membranous nephropathy. Therefore, the development of acute renal injury mediated by acute tubular necrosis or pre-renal haemodynamic effect; glomerular disease mediated by minimal-change disease or membranous nephropathy, acute interstitial nephritis, hyperkalaemia (suggestive of hyporeninemic hypoaldosteronism), hyponatraemia, hypertension, acute papillary necrosis and chronic tubulointerstitial nephritis (analgesic nephropathy) are renal adverse effects of NSAIDs. Some form of nephrotoxicity is developed by an estimated 1 to 5% of the patients treated with NSAIDs.[5,24–27] It is worth mentioning that patients with diabetes mellitus present at high risk for other complications related to NSAIDs such as the presence of gastrointestinal bleeding and cardiac and cerebrovascular events.[28–30]

Despite the adverse effects, NSAIDs are highly effective in certain pathologies and therefore its prescription can be adequate in such cases.[28] However, it is worth mentioning that these should be considered as an alternative treatment, particularly in patients with comorbidities increasing the risk of NSAIDs-associated adverse effects.[28,29]

The use of a representative group of patients of the adult mainland Portuguese population, a three-year study period, large sample of patients, the inclusion of all categories of NSAIDs present in the Portuguese market, the fact that access was given to all prescriptions to patients in the study and the absence of any gaps in data regarding the variables that were analysed as the completion of these data is a condition needed for the issue of prescriptions were considered as strengths of the study design, in addition to the fact that the BDNP database was previously used in studies for the assessment of drug prescription in Portugal.[31]

The fact that only prescriptions issued in mainland Portugal were included in the BDNP database, leaving out those issued in Madeira and in the Azores (collected by independent computer systems) was a limitation of the study. The confirmation on whether or not medication that was

Table 5 – Characteristics of the five leading categories of NSAIDs prescribed to patients with diabetes mellitus, according to healthcare region

NSAIDs	*ARS Norte*	*ARS Centro*	*ARS Lisboa e Vale do Tejo*	*ARS Alentejo*	*ARS Algarve*
1º	Ibuprofen (23.6%)	Ibuprofen (20.0%)	Metamizole (22.8%)	Metamizole (21.5%)	Ibuprofen (18.5%)
2º	Diclofenac (19.0%)	Metamizole (20.0%)	Ibuprofen (19.5%)	Ibuprofen (16.9%)	Metamizole (17.9%)
3º	Etoricoxib (12.0%)	Diclofenac (12.5%)	Diclofenac (14.6%)	Diclofenac (18.0%)	Etoricoxib (14.9%)
4º	Naproxeno (11.5%)	Etoricoxib (12.2%)	Naproxen (11.7%)	Etoricoxib (11.1%)	Diclofenac (13.1%)
5º	Nimesulide (8.7%)	Naproxen (10.4%)	Etoricoxib (10.5%)	Naproxen (10.9%)	Naproxen (8.9%)

NSAIDs: non-steroidal anti-inflammatory drugs; ARS: *Administração Regional de Saúde*

prescribed was in fact acquired and used by patients was not available as data in BDNP only regarded prescribed medications. The record of over-the-counter medications including three of the more prescribed NSAIDs in the market (ibuprofen, naproxen, diclofenac) was also not available from the BDNP database.[32] Therefore, the use of NSAIDs by patients with diabetes mellitus could have been higher than what has been found in the present study, reinforcing the relevance of this analysis. As data on the patient's history are not available from the BDNP database, the presence of diabetes mellitus was inferred by the prescription of oral or injectable hypoglycaemic agents as well as by the presence of presumed renal impairment. Anonymised data on prescriptions issued in Portugal are included in the BDNP database and therefore the identification of patients with presumed renal impairment could only be obtained through medication prescription pattern. Patients who were prescribed oral hypoglycaemic drugs other than metformin that could be used in the presence of GFR decline were selected. Even though insulin is one of the drugs that can be used in patients with renal impairment, patients with diabetes mellitus and presumed renal impairment who were only prescribed insulin were not considered as these could correspond to patients with type-1 diabetes mellitus.[13] Considering that metformin is first-line treatment in type-2 diabetes mellitus and contraindicated in patients with GFR < 30 mL/min/1.73 m^2, the criterion described above was considered as the most adequate with the available data. The reason for drug prescription was not available from BDNP database. ACE-I/ARBs could have been prescribed by different reasons, namely due to their effect on reducing arterial pressure and proteinuria. Likewise, the identification of the reasons for prescribing NSAIDs was not available and therefore NSAIDs could have been correctly prescribed.

Further studies on the use of over-the-counter NSAIDs will be clearly relevant, in addition to the evaluation on any seasonal pattern of their use. The assessment of the impact of a change in NSAIDs prescription pattern to patients with diabetes mellitus on the incidence of adverse effects of this drug class as well as on the incidence of CKD / CKD progression is relevant from the public health point of view.

CONCLUSION

High NSAIDs prescribing rate has been found in patients with diabetes mellitus in Portugal, with a relevant contribution to the high prevalence of end-stage renal disease. Our findings suggested the lack of concern by prescribing physicians towards lowering the use of NSAIDs in patients with diabetes mellitus treated with ACE-I/ARBs and/or presenting with renal impairment. NSAIDs prescribing to patients with diabetes mellitus in Portugal could potentially be reduced, particularly to subgroups of patients with higher prescription rates and at high risk for CKD or CKD progression. Patients with diabetes mellitus, mainly subgroups of high-risk patients will benefit from the implementation of strategies for the encouragement of reducing NSAIDs use, as suggested by our findings. Further studies aimed at the assessment of the impact of measures on the promotion of changes in prescription patterns are clearly relevant.

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HUMAN AND ANIMAL PROTECTION

The authors declare that the followed procedures were according to regulations established by the Ethics and Clinical Research Committee and according to the Helsinki Declaration of the World Medical Association.

DATA CONFIDENTIALITY

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

CONFLICTS OF INTEREST

The authors declare that there were no conflicts of interest in writing this manuscript.

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REFERENCES

1. Portuguese Society of Nephrology. Portuguese Registry of Dialysis and Transplantation. Lisboa: PSN; 2017.
2. Vinhas J, Gardete-Correia L, Boavida JM, Raposo JF, Mesquita A, Fona MC, et al. Prevalence of chronic kidney disease and associated risk factors, and risk of end-stage renal disease: data from the PREVADIAB study. Nephron Clin Pract. 2011;119:c35–40.
3. Nolasco F, Loureiro A, Ferreira A, Macário F, Barata JD, Sá HO, et al. Rede Nacional de Especialidade Hospitalar e de Referenciação. 2017. [acedido 2018 mai 05]. Disponível em: https://www.sns.gov.pt/wp-content/uploads/2017/06/RNEHR-Nefrologia-Aprovada-19-06-2017.pdf.
4. Nissen SE, Yeomans ND, Solomon DH, Lüscher TF, Libby P, Husni ME, et al. Cardiovascular safety of celecoxib, naproxen, or ibuprofen for arthritis. N Engl J Med. 2016;375:2519–29.
5. Perazella MA, Shirali A. 37 - Kidney disease caused by therapeutic agents. In: Gilbert SJ, Weiner DE, editors. National Kidney Foundation Primer on Kidney Diseases. 6th ed. Philadelphia: W.B. Saunders; 2014. p. 326–36.
6. Hörl WH. Nonsteroidal anti-Inflammatory drugs and the kidney. Pharmaceuticals. 2010;3:2291–321.
7. American Society of Nephrology. Avoid nonsteroidal anti-inflammatory drugs (NSAIDS) in individuals with hypertension or heart failure or CKD of all causes, including diabetes. 2012; [acedido 2018 mai 05]. Disponível em: http://www.choosingwisely.org/clinician-lists/american-society-nephrology-nsaids-in-individuals-with-hypertension-heart-failure-or-chronic-kidney-disease/
8. Areia M, Pereira AD, Banhudo A, Coutinho G. Non-steroidal anti-inflammatory drugs and gastroprotection gap among family physicians: results from a survey. GE J Port Gastrenterol. 2013;20:243–9.
9. Ferreira R. Consumo crónico de medicamentos na população de um Centro de Saúde. Rev Port Clin Geral. 2007;23:125-32.
10. Monteiro C, Miranda C, Brito F, Fonseca C, Araujo A. Consumption

patterns of NSAIDs in central Portugal and the role of pharmacy professionals in promoting their rational use. Drugs Therapy Perspectives. 2017;33:32–40.
11. Autoridade Nacional do Medicamento e Produtos de Saúde (INFARMED). Estatística do medicamento e produtos de saúde. 2014. [acedido em 2018 mai 05]. Disponível em: http://www.infarmed.pt/documents/15786/1229727/Estat%C3%ADstica+do+Medicamento+2014/988074f4-4f89-4a7c-9055-844cb88e93fd?version=1.2.
12. Nunes AP, Costa IM, Costa FA. Determinants of self-medication with NSAIDs in a Portuguese community pharmacy. Pharm Pract. 2016;14:648.
13. Abou-Saleh A, Bain SC, Goldsmith DJA. Chapter 32 - Management of the Diabetic Patient with Chronic Kidney Disease. In: Feehally J, Floege J, Tonelli M, Johnson RJ, editors. Comprehensive Clinical Nephrology. 6th ed. Filadelfia: Elsevier; 2018. p.385–95.
14. American Diabetes Association. 8. Pharmacologic approaches to glycemic treatment:standards of medical care in diabetes-2018. Diabetes Care. 2018;41:S73–85.
15. Autoridade Nacional do Medicamento e Produtos de Saúde (INFARMED). Prontuário terapêutico [Internet]. [acedido 2018 mai 05]. Disponível em: http://app10.infarmed.pt/prontuario/index.php.
16. Prazeres F, Santiago L. Prevalence of multimorbidity in the adult population attending primary care in Portugal: a cross-sectional study. BMJ Open. 2015;5:e009287.
17. Prazeres F, Santiago L. The knowledge, awareness, and practices of Portuguese general practitioners regarding multimorbidity and its management: qualitative perspectives from open-ended questions. Int J Environ Res Public Health. 2016;13:1097.
18. Prazeres F, Santiago L. Relationship between health-related quality of life, perceived family support and unmet health needs in adult patients with multimorbidity attending primary care in Portugal: a multicentre cross-sectional study. Health Qual Life Outcomes. 2016;14:156.
19. Direção Geral da Saúde. Programa Nacional de Controlo da Dor. Lisboa: DGV; 2008.
20. Wei L, MacDonald TM, Jennings C, Sheng X, Flynn RW, Murphy MJ. Estimated GFR reporting is associated with decreased nonsteroidal anti-inflammatory drug prescribing and increased renal function. Kidney Int. 2013;84:174–8.
21. Plantinga L, Grubbs V, Sarkar U, Hsu CY, Hedgeman E, Robinson B, et al. Nonsteroidal anti-inflammatory drug use among persons with chronic kidney disease in the United States. Ann Fam Med. 2011;9:423–30.
22. Meuwesen WP, du Plessis JM, Burger JR, Lubbe MS, Cockeran M. Prescribing patterns of non-steroidal anti-inflammatory drugs in chronic kidney disease patients in the South African private sector. Int J Clin Pharm. 2016;38:863–9.
23. Markowitz GS, Bomback AS, Perazella MA. Drug-induced glomerular disease: direct cellular injury. Clin J Am Soc Nephrol. 2015;10:1291–9.
24. Awdishu L, Mehta RL. The 6R's of drug induced nephrotoxicity. BMC Nephrol. 2017;18:124.
25. De Broe ME, Elseviers MM. Over-the-counter analgesic use. J Am Soc Nephrol. 2009;20:2098–103.
26. Ibáñez L, Morlans M, Vidal X, Martínez MJ, Laporte J-R. Case-control study of regular analgesic and nonsteroidal anti-inflammatory use and end-stage renal disease. Kidney Int. 2005;67:2393–8.
27. Perneger TV, Whelton PK, Klag MJ. Risk of kidney failure associated with the use of acetaminophen, aspirin, and nonsteroidal antiinflammatory drugs. N Engl J Med. 1994;331:1675–9.
28. Felson DT. Safety of nonsteroidal antiinflammatory drugs. N Engl J Med. 2016;375:2595–6.
29. Day RO, Graham GG. Non-steroidal anti-inflammatory drugs (NSAIDs). BMJ. 2013;346:f3195.
30. Kim J, Lee J, Shin CM, Lee DH, Park B-J. Risk of gastrointestinal bleeding and cardiovascular events due to NSAIDs in the diabetic elderly population. BMJ Open Diabetes Res Care. 2015;3:e000133.
31. Sousa DC, Leal I, Nascimento N, Marques-Neves C, Tuulonen A, Abegão Pinto L. Use of ocular hypotensive medications in Portugal: PEM Study: a cross-sectional nationwide analysis. J Glaucoma. 2017;26:571–6.
32. Autoridade Nacional do Medicamento e Produtos de Saúde (INFARMED).Medicamentos não sujeitos a receita médica (MNSRM). [Internet]. [acedido 2018 fev 04]. Disponível em: http://www.infarmed.pt/web/infarmed/entidades/licenciamentos/locais-de-venda-mnsrm/lista_de_mnsrm.