

# Systematic Review on the Safety of Concomitant Use of Hypoglycemia-Inducing Drugs and Non-Steroidal Anti-Inflammatory Drugs in Patients With Musculoskeletal Pathology

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**Objectives:** To analyze the safety of combining non-steroidal anti-inflammatory drugs (NSAID) and hypoglycemia-inducing drugs.

**Methods:** A systematic review following a sensitive search strategy was performed. All articles published in MEDLINE (since 1961), EMBASE (since 1961), and Cochrane Library, up to December 2007, were examined. Selection criteria: the population (subjects taking hypoglycemia-inducing drugs: insulin or oral antidiabetic drugs [OAD]), the intervention (concomitantly use of NSAID), and the outcomes related to safety (gastrointestinal, renal, cardiovascular toxicity) and glycemic control. Titles and abstracts of retrieved articles meeting inclusion criteria from the search were reviewed. Only randomized controlled trials (RCT), or cohort studies were included.

**Results:** A total of 33 studies were reviewed in detail, and 11 were finally included, 10 low quality RCT, and 1 prospective cohort study with moderate quality, which included 199 patients. All patients were diabetics; mostly young or middle aged men, on different NSAID and hypoglycemic drugs. There was no evidence of important changes in patient's glycemic controls, nor in their renal function, when combining NSAID with hypoglycemia-inducing drugs. Moreover, there is no clear increase in the number of serious side effects.

**Conclusions:** According to the published evidence, there are not enough arguments to contraindicate the use of NSAID with hypoglycemia-inducing drugs (insulin or OAD).

**Key words:** Non-steroidal anti-inflammatory drugs. Steroids. Hypoglycemia-inducing drugs.

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## Revisión sistemática sobre la seguridad del uso concomitante de fármacos hipoglucemiantes y antiinflamatorios no esteroideos en pacientes con enfermedad reumática

**Objetivos:** Analizar la seguridad del uso concomitante de antiinflamatorios no esteroideos (AINE) y fármacos hipoglucemiantes que permita la toma de decisiones en este sentido en la práctica diaria.

**Métodos:** Revisión sistemática. Se definió una estrategia de búsqueda bibliográfica sensible en MEDLINE (desde 1961), EMBASE (desde 1980) y Cochrane Library hasta diciembre de 2007, definiendo la población (sujetos en tratamiento con fármacos hipoglucemiantes, tanto insulina como antidiabéticos orales [ADO]), la intervención (tratamiento concomitante con AINE) y los resultados (variables relacionadas con la seguridad –toxicidad gastrointestinal, renal o cardiovascular– y con el control glucémico). Se seleccionaron ensayos clínicos (EC) y estudios de cohortes de calidad.

**Resultados:** Se encontraron 33 estudios para analizar en detalle, de los cuales finalmente se incluyeron 11 en los análisis, de los que 10 fueron EC, en general de baja calidad, y 1 estudio de cohortes prospectivas de calidad moderada, que en total incluyeron a 199 pacientes. Todos los pacientes eran diabéticos, la mayoría varones jóvenes o de mediana edad en tratamiento con diferentes AINE y fármacos hipoglucemiantes. El uso de AINE con fármacos hipoglucemiantes no parece estar claramente asociado a cambios importantes en el control glucémico de estos pacientes ni se ha visto que altere significativamente su función renal. Tampoco se ha constatado que esta asociación aumente el número de eventos adversos graves.

**Conclusiones:** Por la evidencia obtenida, no encontramos argumentos suficientes que claramente contraindiquen, debido a efectos secundarios, el uso concomitante de AINE e hipoglucemiantes (tanto ADO como insulina).

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**Palabras clave:** Antiinflamatorios no esteroideos. Esteroides. Hipoglucemiantes.

## Introduction

The use of non-steroidal anti-inflammatory drugs (NSAID) is very frequent in patients with musculoskeletal disease.

Different studies have shown the relationship of NSAID with gastrointestinal complications, some potentially severe such as ulcers, hemorrhage, or digestive tract perforation.<sup>1</sup> On the other hand, in the same way it has been demonstrated that NSAID consumers have other possible independent risk factors for these digestive complications and adverse events of some other nature.

Among others, advanced age, a history of gastroduodenal ulcers or the use of other drugs such as anticoagulants,<sup>2</sup> have been considered.

With relation to the less frequent or less studied adverse events related to NSAID, the medical literature and some pharmacokinetics studies point to the possibility of the appearance of severe hypoglycemia due to NSAID use in patients undergoing treatment with hypoglycemic drugs. Acute renal failure and lactic acidosis cases have also been described.<sup>3-5</sup>

Because in rheumatology it is frequent to follow cases with rheumatic disease who also are undergoing treatment with hypoglycemic drugs, both oral antidiabetics (OAD) and/or insulin, and because it is likely that many of them might merit an NSAID, determining the possible effects of the concomitant use of NSAID and hypoglycemic drugs (especially related with glucose control and renal function) is of great interest in our clinical environment.

Therefore, the objective of this systematic review is to search for published evidence on the concomitant use of NSAID and hypoglycemic drugs in order to contribute to a better management of our patients.

## Material and Methods

A systematic review was done to analyze the safety of the concomitant use of NSAID and hypoglycemic drugs. The selection criteria for the studies were: *a*) studies in which patients took hypoglycemic drugs (both OAD and insulin), without restrictions regarding type, dose or administration route of the hypoglycemic drug; *b*) studies in which the patients, in addition to hypoglycemic drugs, concomitantly took and NSAID, without restrictions regarding the type and dose of NSAID, but excluding studies in which the subjects took NSAID at an

antiplatelet dose and not for analgesia and/or anti-inflammatory purposes, as well as topical treatments; *c*) to evaluate the safety of the simultaneous use of these medications we included studies that analyzed the following variables: gastrointestinal, renal, cardiovascular or glycemic control (fasting and postprandial serum glucose or glycosylated hemoglobin); and *d*) clinical trials (CT) and cohort studies (prospective or retrospective), excluding those studies that only presented pharmacokinetic and/or pharmacodynamic data, as well as studies in healthy volunteers and in animals. Regarding the language, articles in english and spanish were selected. The following electronic databases were searched, up until December 2007: MEDLINE (from 1960), EMBASE (from 1980), and the Cochrane Library (Central). Both MeSH and free text formats were searched. No limits were set for the publication dates. The specific search strategies are detailed in Tables 1 and 2. No manual searches of national (SER) or international (ACR, EULAR) meetings was carried out, due to the great volume of abstracts recovered from the electronic databases.

A single reviewer analyzed the resulting papers, as well as carried out the detailed analysis of those articles included. The results of the search was first thinned out by title and abstract, or by reading the whole article in the case it lacked an abstract, in 20 minute sessions maximum. Articles which explicitly examined the use of NSAID and hypoglycemic drugs were selected for a detailed review, as well as those dealing with the concomitant treatment of comorbid states. After this process, the remaining articles were analyzed in detail. Finally, a manual search with the references of the selected articles was carried out for their detailed analysis. All of the references were recovered from the internet and introduced into Procite 5.1 software in order to ease their management.

To evaluate the methodological quality of the included studies, a Jadad<sup>6</sup> score (1 to 5, was used, considering articles of good quality those with a Jadad score of 3-5) for the CT and the Oxford quality score for the cohort studies.

## Results

The results of the search are detailed in Figure 1. Of the recovered articles, for their detailed analysis, 11 were finally included; 10 are CT<sup>7-16</sup> and 1, a prospective cohort study.<sup>17</sup> The main results of the included studies will be discussed in the following paragraphs (Table 3). The list of excluded articles<sup>18-36</sup> and the cause for their exclusion are detailed in Table 4. Of the 36 articles selected for their detailed review, 28 explicitly analyzed the concomitant use of NSAID and hypoglycemic drugs, the rest (8) did not, but 3 of them provided enough information for their inclusion.

**TABLE 1. Search Strategy and Articles Recovered From MEDLINE**

#	Search Strategy	Results
1	diabetes mellitus OR Insulin OR hypoglicemics OR Agents, Hypoglycemic OR Hypoglycemic Drugs OR Hypoglycemics OR Antidiabetics OR Antidiabetic Agents OR Antidiabetic Drugs OR sulfonylurea OR metformin OR pioglitazone OR rosiglitazone OR glibenclamide OR glicazide OR glimepiride OR glipizide OR repaglinide OR nateglinide OR acarbose OR miglitol OR gliquidona OR tolbutamide OR butformine	405 222
2	NSAID OR Nonsteroidal Anti-Inflammatory Agents OR Nonsteroidal Antiinflammatory Agents OR Analgesics, Anti Inflammatory OR Non-Steroidal Anti-Rheumatic Agents OR Non-Steroidal Antirheumatic Agents OR Aspirin-Like Agents OR Agents, Aspirin-Like OR naproxen* OR ibuprofen* OR dexibuprofen OR dexketoprofen OR flurbiprofen OR Ketoprofen OR Ketorola* OR aceclofenac OR diclofenac OR lornoxicam OR meloxicam OR piroxicam OR tenoxicam OR indometacin OR sulindac OR tolmetin OR fenilbutazon OR Phenylbutazone OR nabumeton OR celecoxib OR etoricoxib OR parecoxib OR rofecoxib OR valdecoxib OR lumiracoxib OR salicylic acid OR acetylsalicylic acid OR diflunisal OR Cyclooxygenase 2 Inhibitors OR COX-2 Inhibitors OR COX2 Inhibitors, OR Coxibs	150 391
3	Randomized [All Fields] OR random allocation*[TIAB] NOT Medline[SB] OR "random allocation"[MeSH Terms] OR randomized [Text Word] OR controlled[All Fields] AND ("clinical trials as topic"[MeSH Terms] OR trial[Text Word]) OR placebo OR blinded	819 404
4	#1 AND #2 AND #3	2430
5	acute [All Fields] OR acute OR post-operative [All Fields] OR post-surgical[All Fields] OR postsurgical [All Fields] [All Fields]OR postoperative OR Postoperative Complications [Mesh] OR intraoperative [All fields] OR Intraoperative Complications [Mesh] dysmenorrhoea[All Fields] OR dysmenorrhoea OR orthodontic [All fields]	28 328
6	#4 NOT #5	2411
7	#6 LimitsLimits: Humans, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Clinical Trial, Phase I, Clinical Trial, Phase II, Clinical Trial, Phase III, Clinical Trial, Phase IV, Comparative Study, Controlled Clinical Trial, English, Spanish	465

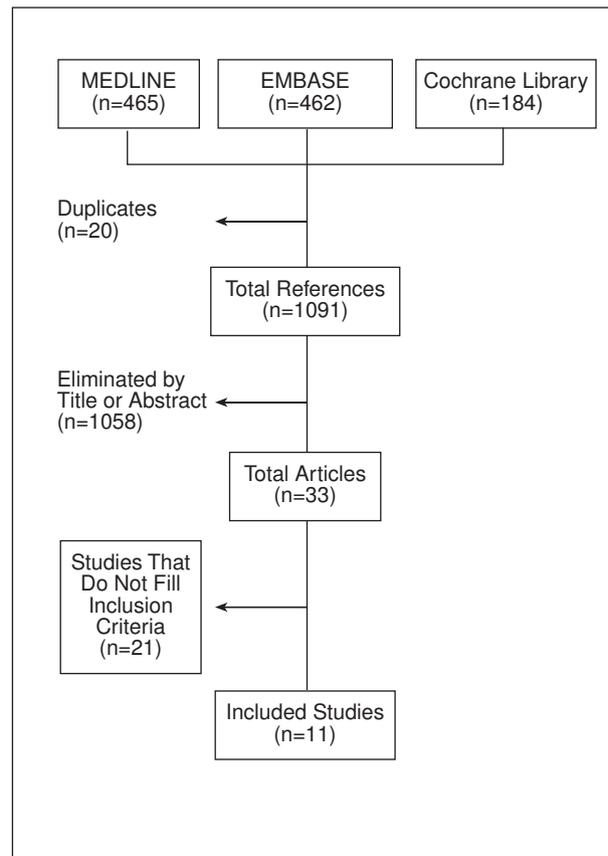
### Summary of the Evidence in NSAID With Hypoglycemic Drugs

As has been commented, 11 articles were included, 10 CT, generally low regarding quality (9 were Jadad 1 or 2 and only 1, Jadad 4), and a prospective cohort study of moderate quality (2c). The duration of follow-up varied between 3 days and 3 years. A total of 199 subjects, all diabetic and mostly young or middle aged men, were analyzed. The studies analyzed the safety of the concomitant use of insulin or OAD with different NSAID and all of them at a different dose. Studies were approved by the ethics committees and patients signed informed consent before entry. Most analyzed in detail the evolution of glycemic control in patients and adverse events, at least generally.

Regarding the safety results, not enough evidence was found to contraindicate the concomitant use of NSAID and hypoglycemic drugs. This is based on the fact that no clear association between the combined use of these drugs and the appearance of problems in glycemic control, renal function and severe gastrointestinal events was seen.

### Results in Detail of the Combined Use of NSAID and Hypoglycemic Drugs

The following data stands out among the results of the CT included in the systematic review:



**Figure.** Flow of study selection.

**TABLE 2. Search Strategy and Articles Recovered From EMBASE**

#	Search Strategy	Results
1	exp antidiabetic agent/ or antidiabetic agent.mp. or exp oral antidiabetic agent/ or exp Biguanide Derivative/ or oral antidiabetic agent.mp. or hypoglycemic.mp. or antidiabetics.mp. or acarbose.mp. or exp ACARBOSE/ or metformin.mp. or exp METFORMIN/ or rosiglitazone.mp. or exp ROSIGLITAZONE/ or pioglitazone.mp. or exp PIOGLITAZONE/ or repaglinide.mp. or exp REPAGLINIDE/ or nateglinide.mp. or exp NATEGLINIDE/ or miglitol.mp. or exp MIGLITOL/ or exp GLIBENCLAMIDE/ or glibenclamide.mp. or sulfonylurea.mp. or exp SULFONYLUREA/ or exp Gliclazide/ or glicazide.mp. or exp GLIMEPIRIDE/ or glimepiride.mp. or exp GLIPIZIDE/ or glipizide.mp. or repaglinide.mp. or exp REPAGLINIDE/ or nateglinide.mp. or exp NATEGLINIDE/ or tolbutamide.mp. or exp TOLBUTAMIDE/	150 823
2	nsaid.mp. or Nonsteroid Antiinflammatory Agent/ or Nonsteroidal Anti-Inflammatory Agents.mp. or (coxib or Cyclooxygenase 2 Inhibitor).mp. or Acetylsalicylic Acid/ or Aspirin-Like Agents.mp. or naproxen.mp. or NAPROXEN/ or ibuprofen.mp. or IBUPROFEN/ or dexibuprofen\$.mp. or DEXIBUPROFEN/ or dexketoprofen.mp. or DEXKETOPROFEN/ or flurbiprofen.mp. or FLURBIPROFEN/ or Ketoprofen.mp. or KETOPROFEN/ or KETOROLAC/ or Ketorolac.mp. or aceclofenac.mp. or ACECLOFENAC/ or diclofenac.mp. or DICLOFENAC/ or lornoxicam.mp. or LORNOXICAM/ or meloxicam.mp. or MELOXICAM/ or Piroxicam.mp. or PIROXICAM/ or piroxicam.mp. or TENOXICAM/ or TENOXICAM/ or INDOMETACIN/ or indometacin.mp. or sulindac.mp. or SULINDAC/ or tolmetin.mp. or TOLMETIN/ or Phenylbutazone.mp. or PHENYLBUTAZONE/ or nabumetone/ or nabumeton.mp. or celecoxib.mp. or CELECOXIB/ or etoricoxib.mp. or ETORICOXIB/ or parecoxib.mp. or PARECOXIB/ or rofecoxib.mp. or ROFECOXIB/ or salicylic acid.mp. or Salicylic Acid/ or acetylsalicylic acid.mp. or Acetylsalicylic Acid/ or diflunisal.mp. or DIFLUNISAL/ or valdecoxib.mp. or VALDECOXIB/ or lumiracoxib.mp. or LUMIRACOXIB/	207 945
3	exp clinical trial/ or evidence based medicine/ or outcomes research/ or crossover procedure/ or double blind procedure/ or single blind procedure/ or prospective study/ or major clinical study/ or exp comparative study/ or placebo/ or "evaluation and follow up"/ or follow up/ or randomization/	1 964 112
4	controlled study/ not case control study/	2 568 695
5	3 or 4	3 774 593
6	((clinic\$ adj5 trial\$) or ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj (blind\$ or mask\$)) or random\$ or placebo\$.ti,ab.	489 355
7	5 or 6	3 890 101
8	1 and 2 and 7	17 876
9	perioperative period.mp. or PERIOPERATIVE PERIOD/ or perioperative care.mp. or SURGERY/ or surgery.mp. or SURGICAL TECHNIQUE/ or surgical procedures.mp. or PEROPERATIVE CARE/ or preoperative care.mp. or intraoperative care.mp. or PEROPERATIVE COMPLICATION/ or POSTOPERATIVE COMPLICATION/ or dysmenorrhoea.mp. or Dysmenorrhea/ or orthodontic.mp. or Orthodontics/ or exp malignant neoplastic disease/ or cancer/ or exp metastasis/ or exp mixed tumor/ or exp "neoplasms of uncertain behavior"/ or exp neoplasms subdivided by anatomical site/ or exp "oncogenesis and malignant transformation"/ or exp paraneoplastic syndrome/ or exp "precancer and cancer-in-situ"/ or adolescent.mp. or adolescent/ or hospitalized adolescent/ or juvenile.mp. or juvenile/ or child.mp. or child/ or boy.mp. or boy/ or gifted child/ or girl.mp. or girl/ or handicapped child/ or hospitalized child/ or preschool child/ or school child/ or infant.mp. or infant/ or baby.mp. or baby/ or high risk infant/ or hospitalized infant/ or newborn.mp. or newborn/ or suckling.mp. or suckling/ or pediatric.mp. or review/ or guideline.mp.	3 370 213
10	8 not 9	666 390
11	exp musculoskeletal disease/ or musculoskeletal disease.mp. or rheumatic polymyalgia.mp. or polymyalgia/ or lupus erythematosus systemic.mp. or systemic lupus erythematosus/ or vasculitis/ or vasculitis.mp. or polymyositis.mp. or polymyositis/ or dermatomyositis.mp. or dermatomyositis/	
12	10 and 11	3391
13	Limit 12 to humans, abstracts	462

– In the study by Baggio et al,<sup>7</sup> the use of ITF-128 with insulin, in comparison with insulin monotherapy, did not produce major changes in blood pressure, heart rate, glycemia, glycosylated hemoglobin, glycosuria, or renal function tests

– According to the CT by Christiansen et al,<sup>8</sup> the use of indomethacin 400 mg/day with insulin, in comparison with baseline values, did not significantly modify the glycemia, glycosuria, glycosylated hemoglobin, and renal function

– Cohen et al<sup>9</sup> proved that the use of ibuprophen 2400 mg/day or sulindac 400 mg/day with OAD or insulin, did not lead to changes in glycemia, glycosylated hemoglobin, cholesterol, or renal or liver function. On the other hand, no differences were seen in the number of severe adverse events with NSAID and insulin

– According to the CT by Cunha-Vaz et al,<sup>10</sup> sulindac 400 mg/day with insulin, compared to insulin monotherapy, was not associated with an increase in the number of adverse events

**TABLA 3. Included Studies, Characteristics, and Main Results<sup>a</sup>**

Study	Participants and Intervention	Results
Baggio <sup>7</sup> ; CT placebo control; follow up 165 days; Jadad 2	n=26 IDDM (42% women; mean age, 37 years). IC: albuminuria (15-300 mg/day) >3 years, normal renal function. CE: AHT, other, non-insulin drugs. ITF-182, 2250 mg/day + insulin. Insulin + placebo	In the ITF-182 group there were no statistically significant changes in BP, HR, glycemia, HbA <sub>1c</sub> , glomerular filtration, blood chemistry
Christiansen <sup>8</sup> ; CT double blind, placebo control; follow up, 3 days; Jadad 2	n=9 IDDM (100% males; age, 19-30 years). EC: diabetic microangiopathy, other NSAID. Indomethacin 140 mg/day 3 days + insulin (n=9). Placebo + insulin (n=9)	No statistically significant changes in the indomethacin group in: glycosuria, HbA <sub>1c</sub> , glycemia. In comparison to placebo, no significant differences were seen if GF, GFF, GPF
Cohen <sup>9</sup> ; CT placebo cross-control; 24 week follow-up; Jadad 2	n=18 patients with DM and peripheral neuropathy (100% male; mean age, 58.4 years), 12 with insulin and 6 with oral antidiabetics. EC: other neuropathies, severe claudication. Ibuprofeno 2400 mg/day 8 weeks (n=18). Sulindac 400 mg/day 8 weeks (n=18). Placebo 50 mg/day 8 weeks (n=18). Continued use of antidiabetic drugs	NSAID did not modify: cholesterol, HbA <sub>1c</sub> , postprandial glucose, creatinine, hepatic function, proteinuria 24 h. Mild adverse gastrointestinal events: ibuprophen (n=5), sulindac (n=0) (P<.006), placebo (n=0); graves: ibuprophen (n=1), sulindac (n=0) (P=.243), placebo (n=0)
Cunha-Vaz <sup>10</sup> ; CT double blind placebo control; 6 month follow-up; Jadad 4	n=18 IDDM (28% women; mean age, 34 years; mean duration of DM, 10.3 years). EC: >5 microaneurisms in the posterior pole of the eye, proliferative retinopathy, other serious complications of DM, liver and renal disease, hematologic, cardiovascular, problems, hyperthyroidism, active peptic ulcer or digestive hemorrhage, malignant disease, pregnancy. Sulindac 400 mg/day + insulin 6 months (n=8). Placebo + insulin 6 months (n=10)	Effects on vision: alterations in permeability, sulindac + insulin (6 eyes) versus placebo + insulin (17 eyes) (P<.001); increase in the size of microaneurisms, sulindac + insulin (n=3) versus placebo + insulin (n=2) (P=.184); new microaneurisms, sulindac + insulin (n=1) versus placebo + insulin (n=1) (P=.441). Adverse events: 1 upper digestive tract hemorrhage in the sulindac group.
Hattori <sup>11</sup> ; CT; 3 years follow-up; Jadad 2	n=40 DM2 (49% women; mean age, 60 years). EC: poor glycemic control. Sulindac 200 mg/day (n=16). Control (n=24). Continued use of antidiabetic medication	Non-proliferative diabetic retinopathy: sulindac (n=0), control (n=3) (P=.283). Proliferative diabetic retinopathy: sulindac (n=0), control (n=1) (P=.295). No changes in BP, HbA <sub>1c</sub> nor severe adverse events in the sulindac group.
Hommel <sup>12</sup> ; CT double blind placebo control; 2 week follow-up; Jadad 2	n=8 DM1 insulin dependent with diabetic neuropathy (100% women; mean age, 36 years). Indomethacin 150 mg/day + insulin 3 days (n=8). Placebo + insulin 3 days (n=8)	Compared to placebo, indomethacin reduced in a significant manner: urinary excretion of PGE <sub>2</sub> , GF, albuminuria and fractioned excretion of albumin
Nilsen <sup>13</sup> ; cross CT; 18 days follow-up; Jadad 1	n=8 DM1 insulin independent with microalbuminuria (87,5% women; age, 22-43). EC: HF, liver failure, serious infections. Naproxen 1000 mg/day + insulin 4 days (n=8).	Placebo + insulin 4 days (n=8) In comparison with placebo, naproxen significantly reduced the excretion of prostaglandin E <sub>2</sub> , no differences in the reduction of albumin or the glomerular filtration
Oli <sup>14</sup> ; CT; 11 week follow-up; Jadad 2	n=16 NIDDM + RA/OA/shoulder arthritis (69% women; age, 31-62 years). Piroxicam 40 mg/day + antidiabetics 3-9 weeks (n=16). Placebo + antidiabetics at weeks 1, 2, 10, 11 (n=16)	In comparison with the placebo period, the use of piroxicam was not associated to significant changes in glycemia, glycosuria, weight or adverse events
Pedrazzi <sup>15</sup> ; CT placebo crossed control, 15-day follow-up; Jadad 2	n=24 NIDDM + OA (50% women; mean age, 71). OAD + indoprophen 600 mg/day 4 day (n=12)/ placebo 5 days (n=12). OAD + placebo 4 days (n=12)/ placebo 5 days (n=12)	In comparison with the placebo period, the use of indoprophen was not associated to significant changes in fasting glucose and an oral load of glucose. No adverse events were detected
Shah <sup>16</sup> ; CT; 5 week follow-up; Jadad 2	n=22 controlled NIDDM >6 months + rheumatic ymptoms NSAID (age, 42-69 years). Chlorpropamides (62.5-375 mg/day) + indoprophen 1200 mg/4 weeks (n=11). Chlorpropamide (125-250 mg/day) + phenylbutazone 300 mg/day 4 weeks (n=11)	Phenylbutazone produced a significant reduction in fasting glucose, with no relation to postprandial readings. Indoprophen was not associated to significant changes in baseline or postprandial glucose
Whiting <sup>17</sup> ; Prospective cohorts; 19 day follow-up; quality 2c	n=10 DM. EC: renal, cardiac, hematologic, ophthalmic or liver disease, DBP > 100 mmHg, allergic to suphonamides, OAD or NSAID. Naproxen 750 mg/day 4 days. Tolbutamide 1 g/day 7 days	No statistically significant differences seen in postprandial glucose (P=.9) nor in the nadir (P=.25) with naproxen

<sup>a</sup>AHT indicates arterial hypertension; BP, blood pressure; CT, clinical trial; DBP, diastolic blood pressure; DM, diabetes mellitus; EC, exclusion criteria; FGF, fraction of glomerular filtration; GF, glomerular filtration; HbA<sub>1c</sub>, glycosylated hemoglobin; HR, heart rate; IDDM, insulin dependent diabetes mellitus; NIDDM, non insulin dependent diabetes mellitus; NSAID, non-steroidal anti-inflammatory drugs; OA, osteoarthritis; OAD, oral antidiabetics; PGE<sub>2</sub>, prostaglandin E<sub>2</sub>; RA, rheumatoid arthritis; RPF, renal plasma flow.

**TABLE 4. Excluded Studies (by Author and Publication Date) and Motives for Exclusion<sup>a</sup>**

Study	Motive for Exclusion
Aguilar <sup>18</sup> (1986)	Use of low-dose(antiplatelet) ASA as NSAID
Anderson <sup>19</sup> (2002)	Healthy volunteers
Bakris <sup>20</sup> (1995)	Use of high dose NSAID concomitantly with misoprostole
Chlud <sup>21</sup> (1977)	No relationship with research question
Day <sup>22</sup> (1995)	Healthy volunteers
de Cosmo <sup>23</sup> (1993)	Use of low-dose(antiplatelet) ASA as NSAID
Farker <sup>24</sup> (2002)	No indication on wether hypoglycemic medication is employed
Hartmann <sup>25</sup> (1990)	Healthy volunteer
Haupt <sup>26</sup> (1987)	German language
Kubacka <sup>27</sup> (1986)	Healthy volunteers
Mathiesen <sup>28</sup> (1988)	No new data is given for the review in comparison with that published by another article in the same group of patients (Hommel 1987)
Micossi <sup>29</sup> (1978)	Unclear wether patients received hypoglycemic drugs
Morrison <sup>30</sup> (1982)	Healthy volunteers
Pereira <sup>31</sup> (2000)	No hypoglycemic drugs are employed
Pereira <sup>32</sup> (2001)	No hypoglycemic medication is taken
Pfeifer <sup>33</sup> (1993)	Clear clinical data on efficacy, not safety
Poggi <sup>4</sup> (2006)	No analysis of clinical effect, only pharmacokinetics/dynamics
Price <sup>3</sup> (2003)	Clinical case
Rudberg <sup>34</sup> (1993)	All data is related with intense exercise
Sharma <sup>35</sup> (1989)	Topical NSAID
Shimura <sup>36</sup> (2007)	Topical NSAID

<sup>a</sup>ASA indicates acetyl salicylic acid; NSAID, non-steroidal anti-inflammatory drugs.

– Hattori et al,<sup>11</sup> saw that the use of sulindac 200 mg/day with OAD or insulin did not produce important changes in blood pressure and glycosylated hemoglobin or severe adverse events

– Hommel et al,<sup>12</sup> saw that the use of indomethacin 150 mg/day, in comparison with insulin monotherapy, produced a reduction in the excretion of PGE<sub>2</sub>, glomerular filtration, albuminuria, and fractioned clearance of albumin

– In the study by Nilsen et al<sup>13</sup> it was seen that the use of naproxen 1000 mg/day with insulin, compared to insulin alone, led to a larger reduction in urinary excretion of PGE<sub>2</sub>. No differences were seen in relation to albuminuria and glomerular clearance

– The CT by Oli et al<sup>14</sup> describes that the use of peroxicam 40 mg/day with OAD, compared to OAD without NSAID, was not associated to significant changes in glycemia, glycosuria, weight or other adverse events

– According to Pedrazzi et al,<sup>15</sup> the use of OAD with indoprophen 600 mg/day, in comparison with OAD monotherapy, was not associated to significant changes

in fasting glucose nor after an oral load of glucose and no adverse events were detected

– In the study by Shah et al,<sup>16</sup> the use of chlorpropamide with phenylbutazone 300 mg/day was associated to a significant reduction in fasting glucose, but not in postprandial measurements. On the other hand, the use of OAD with indoprophen was not associated to changes in fasting or postprandial glucose levels

– A cohort study by Whiting et al<sup>17</sup> showed that the use of naproxen 1000 mg/day with tolbutamide 1 g/day did not produce changes in serum glucose nor in its nadir

## Discussion

In this systematic review of the literature, the safety of the concomitant use of NSAID and hypoglycemic drugs (both OAD and insulin) were analyzed. In order to reach this objective, an extensive search of the main available bibliographic databases, as has been described in the

“Material and Methods” section. We only included CT and quality cohort studies, considering that this is the best way to answer the research question. In general, we can consider that the use of NSAID with hypoglycemic drugs does not seem to produce important alterations in glycemic control or on the renal function of patients. We did not find a significant increase in the number of adverse events of another nature, such as gastrointestinal either.

After the detailed analysis, 11 studies were included (10 CT<sup>7-16</sup> and 1 cohort study<sup>17</sup>). The quality of the CT in general was poor, all were Jadad 1 or 2, excepting one that reached a 4 point score. Regarding the included cohort study, it was moderate in quality, 2c on the Oxford score. It represents one of the main limitations of the study which must be kept present when evaluating the conclusions of this review.

As for the patients studied, 199 were included, all of them diabetic and mostly young or middle-aged males. Only 2 studies<sup>15,16</sup> included patients who also had some sort of musculoskeletal disease. Therefore, and given the lack of published evidence with respect to the research question in patients with rheumatic disease, it was finally decided not to restrict the review to this type of patients. This led to, as happened in the case of the quality of the studies, the representativity of the included sample was also limited and does not reflect the spectrum and characteristics of the patients which are normally followed in rheumatology consults. But it is also important to mention that the majority of included patients were young or middle aged, without severe concomitant disease, making the results biased, because these patients can be less predisposed to adverse events.

On the other hand, the NSAID and hypoglycemic drugs studied were diverse, as were the prescribed doses (when recorded) making it difficult to establish comparisons between drug groups.

In relation to the events studied, all of the included articles evaluated glycemic control of patients during follow-up, and most also analyzed clinically relevant and/or severe adverse events such as gastroduodenal ulcer or digestive hemorrhage. In general, these outcome measurements were defined by very similar criteria in all of the studies. As for the results themselves, as has been commented, no evidence of the of problems in glycemic control or renal function by the concomitant use of NSAID and hypoglycemic drugs was seen, as had been indicated by some publications.<sup>3-5</sup> Only one study<sup>16</sup> described that the association of phenylbutazone with OAD produced a significant reduction in fasting glucose (not clinically important). Nor has it been manifested that it produced a larger number of adverse events such as gastrointestinal. In only one study<sup>9</sup> the use of ibuprofen was associated to a larger number of gastrointestinal adverse events, mild in nature, and not associated to an increase in the severe gastrointestinal adverse events.

It is important to note, at this point, that it is occasionally difficult to determine if certain secondary events could be due to the use of NSAID and hypoglycemic drugs, could really be produced by the underlying disease and not its treatments.

Taking into account the limitations found in this systematic review, we consider that other studies are necessary with better methodological quality and more representative, to be able to determine the true effect of the use of NSAID and hypoglycemic drugs, as well as elucidate the possibility that a concrete association of drugs has a better safety profile than others.

Finally, in conclusion, not enough evidence to contraindicate the the concomitant use of NSAID and hypoglycemic drugs was seen, with a 2c degree of evidence and a C/D strength for recommendation.

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