ANNALS OF TRANSPLANTATION

ORIGINAL PAPER

ISSN 1425-9524
© Ann Transplant, 2015; 20: 154-159
DOI: 10.12659/AOT.892067

Received: 2014.07.23
Accepted: 2014.10.21
Published: 2015.03.20

Waist Circumference as an Independent Risk Factor for NODAT

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEFG 1 Ivana Dedinská
G 1 Ľudovít Laca
D 1 Juraj Miklušica
C 2 Jaroslav Rosenberger
DF 3 Zuzana Žilinská
F 4 Peter Galajda
FG 4 Marián Mokáň

1 Surgery Clinic and Transplant Center, University Hospital Martin and Jessenius Faculty of Medicine, Comenius University, Martin, Slovakia
2 Transplant Center, University Hospital of L. Pasteur, Košice, Slovakia
3 Urological Clinic and Center for Kidney Transplantation, University Hospital Bratislava and Faculty of Medicine, Comenius University, Martin, Slovakia
4 Clinic of Internal Medicine I, University Hospital Martin and Jessenius Faculty of Medicine, Comenius University, Martin, Slovakia

Corresponding Author: Ľudovít Laca, e-mail: laca@jfmed.uniba.sk
Source of support: This work was supported by the project "Virtual simulation and training as a new form of learning" to JFM CU in Martin, co-financed from EU ITMS code project 26110230071

Background: New-onset diabetes mellitus after transplantation (NODAT) is a serious and frequent complication of solid organ transplantations. NODAT leads to 2-3 times higher cardiovascular morbidity and mortality. Visceral obesity is a key factor for diabetes mellitus type 2 and metabolic syndrome development, and is an independent risk factor for cardiovascular diseases.

Material/Methods: The series consisted of 167 patients after primary kidney transplantation from a dead donor (64 patients had developed NODAT), average age of the series was 46.1±11.6 years. We retrospectively examined waist circumference, body mass index, and weight gain in the 12th month after transplantation. We examined average level of triglycerides, cholesterol, and immunosuppression throughout the 12 monitored months.

Results: Patients with NODAT were significantly older (P=0.004) and had greater waist circumference (P<0.0001) and higher average sirolimus level (P=0.0262). We identified the following independent risk factors for NODAT by using multivariate analysis: age at the time of transplantation above 50 years (HR=2.5038, [95% CI: 1.7179 to 3.6492], P<0.0001), waist circumference in men greater than 94 cm (HR=1.9492, [95% CI: 1.1697 to 3.2480], P=0.0104) and in women greater than 80 cm (HR=4.5018, [95% CI: 1.8669 to 10.8553], P=0.009). By using correlation coefficient we have proved that greater waist circumference was related to higher incidence of NODAT (r=0.1935, [95% CI: 0.01156 to 0.3630], P=0.0374). Graft survival (death censored) 12 months after kidney transplantation was 97.1% in the control group and 95.3% in the NODAT group (P=0.5381). Patient survival 12 months after kidney transplantation in the control group was 98.1% and in the NODAT group it was 96.9% (P=0.6113).

Conclusions: We identified waist circumference as an independent risk factor for NODAT in our analysis.

MeSH Keywords: Diabetes Mellitus • Immunosuppression • Kidney Transplantation • Waist Circumference

Full-text PDF: http://www.annalsoftransplantation.com/abstract/index/idArt/892067

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

Background

Risk factors of cardiovascular diseases after kidney transplantation are eliminated by restoration of renal functions; however, new risks such as impaired glucose tolerance, diabetes mellitus, artery hypertension, and fat metabolism disorders appear simultaneously. New-onset diabetes mellitus after transplantation (NODAT) is a severe and frequent complication of solid organ transplantations. Incidence of this phenomenon ranges from 4% to 25% according to the transplanted organ, the length of monitoring, and the applied immunosuppressive protocol. Incidence of NODAT 12 months after transplantation is shown in Table 1 [1–4].Glucose regulation disorder in patients after kidney transplantation leads to 2–3 times higher cardiovascular morbidity and mortality compared with non-diabetic patients, and the quality of life is lowered. The risk of cardiovascular diseases (CVD) development in patients with NODAT is also increased by hyperlipidemia, artery hypertension, and smoking. NODAT is also related to other complications such as graft rejection, relapsing infections, and worsened long-term graft function [5]. Besides the well-known long-term complications of diabetes mellitus in patients after kidney transplantation with NODAT (as well with fasting hyperglycemia and impaired glucose tolerance), we can observe graft hyperfiltration, which adversely affects function and survival of the transplanted kidney. This population of patients has faster onset of vascular complications and increased mortality in comparison with "normoglycemic" patients [5–7]. There is increased cardiovascular mortality and morbidity, higher risk of serious infectional and neuropsychic complications, and higher risk of rejection and worsened graft survival in patients after liver transplantation with NODAT [8,9]. There was a higher incidence of cytomegalovirus (CMV) infection and acute rejection among patients with NODAT after lung transplantation, but increased mortality in comparison with patients without NODAT was not recorded in this case [10]. Waist circumference is the most important diagnostic criterion for metabolic syndrome. Waist circumference measurement in clinical practice is a simple measurable factor for risk control. At present, it is preferred to use values of waist circumference greater than 102 cm in men and 88 cm in women as the most convenient method for diagnosing obesity (according to Adult Treatment Panel III), suggesting that the criteria of the International Diabetic Federation (IDF) have clearly recommended different criteria for individual world populations, with a proposal for marginal waist circumference of 94 cm in men and 80 cm in women for the European population as the basic required criterion (Table 2) [11]. Visceral obesity is a key factor for diabetes mellitus type 2 and metabolic syndrome development and is an independent risk factor for cardiovascular diseases. In the original concept of metabolic syndrome, increased adiposity was predominantly

Table 1. Incidence of NODAT.

Transplanted organ	Incidence of NODAT
Kidney	4–25%
Liver	2.5–25%
Heart	4–40%
Lung	30–35%

Table 2. Ethnic specific values for waist circumference [11].

Country/Ethnic group	Waist circumference
Europids, NorthAmericans	Male ≥94 cm, female ≥80 cm
South Asians	Male ≥90 cm, female ≥80 cm
Chinese	Male ≥90 cm, female ≥80 cm
Japanese	Male ≥90 cm, female ≥80 cm
Ethnic South and Central Americans	Use South Asian data
Sub-Saharan Africans	Use European data
Eastern Mediterranean and Middle East (Arab) populations	Use European data

Table 3. Set characteristics.

	Complete set	Men	Women	P value
Average age at the time of KT (years)	46.1±11.6	46.2±11.5	46.0±11.8	0.9147
Average weight gain from KT (kg)	6.5±6.3	6.1±5.6	7.2±7.3	0.2879
Average BMI value (kg/m²)	**27.8±4.7**	**28.4±3.9**	**26.8±5.6**	**0.0364**
Average waist circumference (cm)	**99.1±12.4**	**102.7±9.3**	**92.8±14.6**	**<0.0001**
Average TAG value (mmol/l)	**1.9±0.8**	**2.1±0.9**	**1.7±0.6**	**0.0023**
Average cholesterol value (mmol/l)	4.4±0.8	4.3±0.8	4.5±0.6	0.0930

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

Table 4. ADA diagnostic criteria for diabetes mellitus.

Diagnostic criteria for diabetes mellitus
Symptoms of diabetes mellitus: polyuria, polydipsia, unexplained weight loss or Fasting blood glucose ≥7 mmol/l or Glycemia in the 2nd hour of oGTT ≥11.1 mmol/l

considered to be a secondary consequence of the adipogenic effect of chronic hyperinsulinemia, but currently it is being emphasized that increased adiposity is, together with insulin resistance and hyperinsulinemia, the primary cause of diabetes mellitus and metabolic syndrome. We assume that, as in case of patients with diabetes mellitus type 2, waist circumference will also influence development of NODAT in the population of patients after kidney transplantation [12].

Material and Methods

We retrospectively evaluated selected risk factors for NODAT in a series of 167 patients (Europids) after primary kidney transplantation from a dead donor (in the years 2003–2012) in the Transplant Center Martin. We examined waist circumference, body mass index (BMI), and weight gain from transplantation in the 12th month after transplantation. We further examined the average level of triglycerides (mmol/l) and total cholesterol (mmol/l) throughout 12 months after kidney transplantation and lipid-lowering therapy. We recorded the type of immunosuppression in each patient (tacrolimus, cyclosporin A, or sirolimus) and their average values and average dose of prednisone/day throughout the monitored period (Table 3). According to NODAT development during the monitored period, we assigned the patients to control group (n=103) or NODAT group (n=64). NODAT was diagnosed according to ADA (American Diabetes Association) criteria (Table 4). We used a certified statistical program, MedCalc version 13.1.2,

Table 5. Results.

	Control group n=103	NODAT n=64	P value
Age at the time of KT (years)	**43±11.3**	**52±10**	**0.004**
Weight gain 12 months after KT (kg)	6.5±6.6	4.5±5.7	0.1640
BMI value 12 months after KT (kg/m^2)	27.8±4.8	29±4.7	0.2617
Waist circumference 12 months after KT (cm)	**99±9.5**	**110.8±12.9**	**<0.0001**
Waist circumference 12 months after KT (cm) – men	**102.7±9.4**	**107.6±8**	**0.0007**
Waist circumference 12 months after KT (cm) – women	**92.8±15.6**	**104.4±11.3**	**<0.0001**
Triglycerides value (mmol/l)	2.0±0.7	1.9±0.8	0.5358
Cholesterol value (mmol/l)	4.4±0.7	4.4±0.8	1.000
% patients with tacrolimus (level)	85.6% (4.7 ng/ml)	84.6% (4.8 ng/ml)	0.5592
% patients with cyclosporine (level)	6.7% (86.9 ng/ml)	7.7% (96 ng/ml)	0.7804
% patients with mTOR inhibitors (level)	**7.8% (5.8 ng/ml)**	**7.7% (7.6 ng/ml)**	**0.0262**
dose of prednisone (mg/day)	8.5±2.3	8±2.0	1.000

Table 6. File types under lipid-lowering therapy.

	Control group n=103	NODAT n=64	P value
Statins	54.5%	30.8%	0.0531
Fibrates	3.3%	7.7%	0.6701
Statins + ezetimib	34.5%	57.7%	0.0572
No lipid-lowering therapy	7.7%	3.8%	0.8002

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

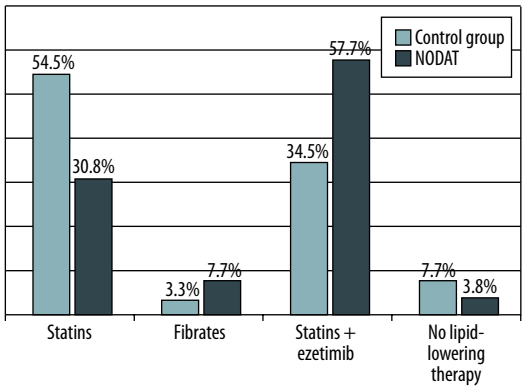

Figure 1. File Types under lipid-lowering therapy.

for statistical evaluation and we used the following statistical analyses: Student's t-test, chi-square test, correlation coefficient, Cox proportional hazard model, and Kaplan-Meier curves of survival. We consider the value P<0.05 to be statistically significant.

Results

From the overall set of patients, 38.2% of patients (n=64) developed NODAT in the monitored period of 12 months after kidney transplantation. Patients in the NODAT group were statistically significantly older age at the time of kidney transplantation (P=0.004), they had significantly greater waist circumference 12 months after kidney transplantation (P<0.0001), and had significantly higher average level of sirolimus (P=0.0262) throughout the 12 monitored months after kidney transplantation. The average levels of triglycerides and cholesterol were without statistically significant differences in both groups (P=0.5358 for triglycerides, P=1.000 for cholesterol) (Table 5). However, in more than 50% of patients (P=0.0572) with NODAT, combined lipid-lowering therapy was necessary for achieving optimal values of lipids (Table 6, Figure 1). We identified the following independent risk factors for NODAT by using multivariate analysis: age at the time of transplantation above 50 years (HR=2.5038, [95% CI: 1.7179 to 3.6492], P<0.0001), waist circumference in men greater than 94 cm (HR=1.9492, [95% CI: 1.1697 to 3.2480], P=0.0104), and waist circumference in women greater than 80 cm (HR=4.5018, [95% CI: 1.8669 to 10.8553], P=0.009) (Table 7). By using correlation coefficient we proved that greater waist circumference was related to higher incidence of NODAT (r=0.1935, [95% CI: 0.01156 to 0.3630], P=0.0374). In the series of patients with NODAT we identified the month after kidney transplantation in which NODAT was diagnosed. We found that NODAT had been diagnosed in a significantly higher number of patients (70%) in the first 6 months after kidney transplantation (P<0.001). We examined NODAT treatment in the series of patients with NODAT. A comparable number of patients were treated with peroral antidiabetics and insulin (42.5%), the fewest patients required combined treatment by peroral antidiabetics and insulin (6.3%), and 8.7% of patients were treated with diet. The value of creatinine 12 months after kidney transplantation was comparable in both groups (P=0.9144) similarly eGFR according to CKD EPI (P=0.0635). Finally, we compared the 12-month graft survival (death censored) and 12-month patient survival. Graft survival 12 months after kidney transplantation was 96.4%; in the control group it was 97.1% and in the NODAT group it was 95.3%, but we did not prove a statistical difference (P=0.5381) (Figure 2). Patient survival 12 months after KT was 97.6%; in the control group it was 98.1% and in the NODAT group it was 96.9%, but we did not prove a statistical difference (P=0.6113) (Figure 3). In the 12-month monitoring we identified patients whose death was caused by CVS diseases. Death was caused by CVS stroke in 50% of cases in the control group and in the group of patients with NODAT it was 100% of cases (P=0.1441).

Table 7. Multivariate analysis.

	Hazard ratio	CI 95%	P value
Age at the time of KT<30 years	0.3065	0.08265–1.1363	0.0769
Age at the time of KT 31–39 years	0.5000	0.0526–4.7518	0.5714
Age at the time of KT 40–49 years	0.7000	0.4292–1.1416	0.1529
Age at the time of KT 50–59 years	**2.5038**	**1.7179–3.6492**	**<0.0001**
Age at the time of KT ≥60 years	**1.1376**	**1.0437–1.2399**	**0.0034**
Waist circumference 12 months after KT ≥94 cm (men)	**1.9492**	**1.1697–3.2480**	**0.0104**
Waist circumference 12 months after KT ≥80 cm (women)	**4.5018**	**1.8669–10.8553**	**0.009**
Level of sirolimus <6 ng/ml	0.2400	0.01467–3.9265	0.3169
Level of sirolimus ≥6 ng/ml	4.1667	0.2547–68.1682	0.3169

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

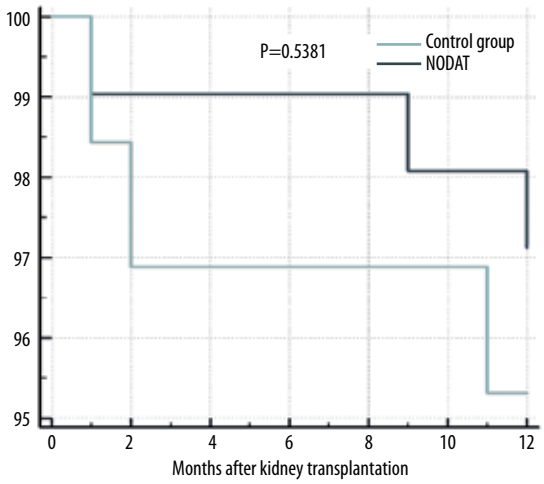

Figure 2. 12-month graft survival (death censored)

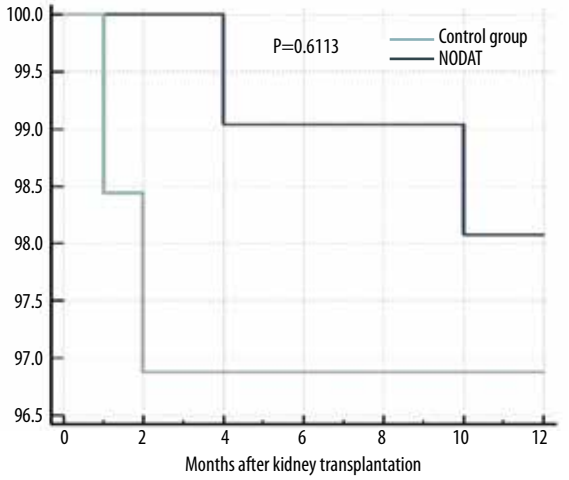

Figure 3. 12-month patient survival.

Discussion

In agreement with our results, age at the time of KT has been reported to be an independent risk factor for NODAT in other studies. Cosio et al. found up to 2.2 times higher risk of NODAT development in recipients older than 45 years compared with younger recipients [13]. Similarly, USRDS data show a strong relationship between age of recipient and NODAT development. Recipients age 45–59 years had 1.9 times higher risk of NODAT than recipients age 18–33 years. In recipients older than 60 years, the risk of NODAT development was double that of younger recipients [14]. As the basic criterion for metabolic syndrome, waist circumference ≥94 cm in men and ≥80 cm in women (according to IDF criteria for men) was evaluated as an independent risk factor for NODAT in our analysis. A stronger relationship between waist circumference and cardiovascular morbidity and mortality was shown by several analyses in comparison with BMI in non-transplanted population. According to Czernichov et al., waist circumference is a stronger predictor of cardiovascular mortality (hazard ratio [95% CI]: 1.15 [1.04–1.27] than BMI [15]. Our analysis indicates that we may expect this phenomenon also in the transplanted population. By using univariate analysis, Kodgire et al. found statistically significantly greater waist circumference at the time of kidney transplantation in a series of 50 patients after kidney transplantation from a living donor in the group of patients who had developed NODAT in the 12-month monitored period after kidney transplantation [16]. We also confirmed correlation between waist circumference and NODAT incidence. Studies comparing the relationship between waist circumference and risk of NODAT development, or the risk of CVS morbidity or mortality in patients after kidney transplantation are not available. However, considering data from the population of non-transplanted patients, further analyses are necessary. We have not proved a statistically significant difference between the values of cholesterol and TAG in the series of patients with NODAT in comparison with the control group. The results may, however, be affected by hypolipidemic therapy. In the control group, 54.5% of patients were administered statin and 34.5% were administered combined therapy (statin + ezetimibe) and in the NODAT group it was up to 57.7% of patients who were treated with combined hypolipidemic therapy. In a retrospective analysis by Porrini et al., hyperlipidemia before transplantation was assessed as a risk factor for NODAT, but only in the group of recipients who were administered tacrolimus. Hyperlipidemia is closely linked to insulin resistance and, consequently, to NODAT development [6,17]. The type of immunosuppression did not show as a risk factor for NODAT development in our observation, which we put into the context of a very small group of patients receiving cyclosporine or mTOR inhibitors. Graft and patient survival was numerically lower in the NODAT group in our analysis (without statistical significance), which is probably related to the short follow-up time. NODAT decreases long-term allograft survival. Most, if not all, of the adverse effect on allograft survival is due to the increased mortality associated with NODAT. For example, in a retrospective analysis of 27 707 transplant recipients, NODAT was associated with increased risk of allograft failure from any cause but not for death-censored graft loss (or graft loss without death) [18]. The mechanism by which NODAT may decrease allograft survival independent of increased mortality is not clear. Some have suggested that the recurrence of diabetic nephropathy may contribute to the increased rate of graft failure without death. Another possibility is that efforts to decrease diabetogenic immunosuppressive therapy to prevent NODAT and its complications may increase rates of rejection [14].

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

Conclusions

We identified waist circumference as an independent risk factor for NODAT in our analysis. Waist circumference measurement is simple and accessible. Regular weight and waist circumference control in patients after kidney transplantation leads to identification of patients at risk for NODAT. Screening for risk factors for diabetes mellitus should be done even before placing a patient on the waiting list, and it is advisable to also perform the oral glucose tolerance test (oGTT) in patients with physiological levels of fasting glycemia. Patients on the waiting list who have risk factors for diabetes mellitus should therefore be informed of their elimination (e.g., weight control, diet, exercise). In addition to this, patients should cease smoking, control blood pressure, and improve their lipoprotein profile [19].

References:

1. Davidson J, Wilkinson AH, Dantal J et al: New-onset diabetes after transplantation: 2003 International Consensus Guidelines. Transplantation, 2003; 7: SS3–24
2. Baid S, Cosimi AB, Farrel ML et al: Posttransplant diabetes mellitus in liver transplant recipients: risk factors, temporal relationship with hepatitis C virus allograft hepatitis, and impact on mortality. Transplantation, 2001; 72: 1066–72
3. Knobler H, Stagnaro-Green A, Wallenstein S et al: Higher incidence of diabetes in liver transplant recipients with hepatitis C. J Clin Gastroenterol, 1998; 26: 30–33
4. Ye X, Kuo H-T, Sampaio MS et al: Risk factors for the development of new-onset diabetes mellitus after transplant in adult lung transplant recipients. Clin Transplant, 2010; 1111: 1–7
5. Hjelmesaeth J, Hartmann A, Leivestad T: The impact of early-diagnosed new-onset post-transplantation diabetes mellitus on survival and major cardiac events. Kidney Int, 2006; 69: 588–95
6. Cosio FG, Pesavento TE, Kim S et al: Patient survival after renal transplantation. IV. Impact of post-transplant diabetes. Kidney Int, 2002; 62: 1440–46
7. Porrini E, Delgado P, Torres A: Metabolic syndrome, insulin resistance, and chronic allograft dysfunction. Kidney Int Suppl, 2010; 119: S42–46
8. Moon JI, Barbeito R, Faradji RN et al: Negative impact of new onset diabetes mellitus on patient and graft survival after liver transplantation: long-term follow-up. Transplantation, 2006; 82: 1625–28
9. John PR, Thuluvath PJ: Outcome of patients with new-onset diabetes mellitus after liver transplantation compared with those without diabetes mellitus. Liver Transpl, 2002; 8: 708–13
10. Ollech JE, Kramer MR, Peled N et al: Post-transplant diabetes mellitus in lung transplant recipients: incidence and risk factors. Eur J Cardiothorac Surg, 2008; 33: 844–48
11. The IDF consensus worldwide definition of the metabolic syndrome, International diabetes federation 2006
12. Galajda P, Mokáň M: Problematika etiopatogenézy a diagnostiky metabolického syndrómu. Diabetes a obezita, 2004; 4(7): 39–49 [in Slovakian]
13. Cosio FG, Pesavento TE, Osei K et al: Post-transplant diabetes mellitus: increasing incidence in renal allograft recipients transplanted in recent years. Kindey Int, 2001; 59(2): 732–37
14. Kasiske BL, Snyder JJ, Gilbertson D, Matas AJ: Diabetes mellitus after kidney transplantation in the United States. Am J Transplant, 2003; 3: 178–85
15. Czernichow S, Kengne AP, Stamatakis E et al: Body mass index, waist circumference and waist – hip ratio: which is the better discriminator of cardiovascular disease mortality risk? Evidence from an individual-participant meta-analysis of 82 864 participants from nine cohort studies. Obesity Reviews, 2011; 12(9): 680–87
16. Kodgire S, Varughese S, Basu G et al: Clinical profile of New Onset Diabetes Mellitus After Transplant (NODAT) in renal allograft recipients. Moderated Poster Session: Clinical Studies in Renal Transplantation, 2013
17. Porrini E, Delgado P, Alvarez A et al: The combined effect of pretransplant triglyceride levels and the type of calcineurin inhibitor in predicting the risk of new onset diabetes after renal transplantation. Nephrol. Dial. Transplant, 2008; 23: 1436–41
18. Cole EH, Johnston O, Rose CL et al: Impact of acute rejection and new-onset diabetes on long-term transplant graft and patient survival. Clin J Am Soc Nephrol, 2008; 3: 814–21
19. Wilkinson A, Davidson J, Dotta F: Guidelines for the treatment and management of new-onset diabetes after transplantation. Clin Transplant, 2005; 19: 291–98

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]