Dedinská et al., J Metabolic Synd 2016, 5:2
DOI: 10.4172/2167-0943.1000205

Journal of Metabolic Syndrome
ISSN: 2167-0943

Research Article Open Access

Correlation between CMV Infection and NODAT

Dedinská I[1], Stančík M[2]*, Laca L[1], Miklušica J[1], Kantárová D[2], Ulinako J[3], Janek J[4], Galajda P[2] and Mokáň M[2]

[1]Surgery Clinic and Transplant Center, University Hospital Martin and Jessenius Faculty of Medicine, Comenius University, Slovak Republic
[2]Clinic of Internal Medicine I, University Hospital Martin and Jessenius Faculty of Medicine, Comenius University, Slovak Republic
[3]Department of Plastic Surgery, F.D.Roosevelt's Faculty Hospital in Banská Bystrica, Slovak Republic
[4]Department of Vascular Surgery, F.D.Roosevelt's Faculty Hospital in Banská Bystrica, Slovak Republic

Abstract

Purpose: New-onset diabetes mellitus after transplantation (NODAT) is a well-known complication of transplantation.

Materials and methods: Retrospectively, we detected CMV replication (PCR) in every month after transplantation of kidney in the first 12 months after transplantation in patients in a homogenous group from the aspect of immunosuppresion.

Results: In the group of 167 patients (control group: n = 103, NODAT group: n = 64), the average value of CMV viremia was without any significant difference between the NODAT group and the control group (P = 0.9285). In the 10th month after kidney transplantation, we recorded significantly higher CMV viremia in the NODAT group (p < 0.0001), however, in the multi variant analysis, that difference was not confirmed. Thus, in our group, CMV is of no relevance with the development of NODAT in the monitored period. The survival of patients and graft was 12 months after kidney transplantation without any statistically significant difference between the monitored groups (P = 0.6113 - survival of the patient; P = 0.5381 – survival of the graft).

Conclusion: Our analysis shows that in regular monitoring of CMV viremia and applying chemoprophylaxison the risk recipeints, CMV is not the risk factor for NODAT.

Keywords: Cytomegalovirus; New-onset diabetes after transplantation; Kidney transplantation; Chemoprophylaxis; Immunosuppressive drugs

Introduction

New-onset diabetes mellitus after transplantation (NODAT) is a well-known complication of transplantation and its development is associated with lower graft function and survival and reduced long-term patient survival mainly because of cardiovascular events [1-3]. Kidney transplant recipients who develop NODAT have variably been reported to be at increased risk of fatal and nonfatal cardiovascular events and other adverse outcomes including infection, reduced patient survival, graft rejection, and accelerated graft loss compared with those who do not develop diabetes. Identification of high-risk patients and implementation of measures to reduce the development of NODAT may improve the long-term patient and graft outcome [4]. In 2003, the International Expert Panel consisting of experts from both the transplant and diabetes fields set forth the International Consensus Guidelines for the diagnosis and management of NODAT [5,6]. It was recommended that the definition and diagnosis of NODAT should be based on the definition of diabetes mellitus and impaired glucose tolerance (IGT) described by the World Health Organization (WHO) [6,7]. The American Diabetes Association (ADA) guidelines for the diagnosis diabetes mellitus are provided in Table 1 [4].

Cytomegalovirus (CMV) is one of the most important infections in renal transplant recipients [8-12]. Exposure to the virus, as indicated by presence of detectable immunoglobulin G (IgG) anti-CMV antibodies in the plasma, increases with age in the general population and is present in more than two-thirds of donors and recipients prior to transplantation [8]. It is therefore common for the donor and/or recipient to be CMV-positive at the time of transplantation.

CMV can be transmitted from the donor either by blood transfusion or by the transplanted kidney; the concurrent administration of immunosuppressive drugs to prevent rejection further increases the risk of clinically relevant CMV disease, with induction therapy principally being associated with an increased risk of disease [13,14]. Thus, both the recipient and the donor are routinely tested for anti-CMV antibodies prior to transplantation. CMV disease may manifest as a nonspecific febrile syndrome (e.g. fever, leukopenia, and atypical lymphocytosis) or tissue-invasive infections (e.g. hepatitis, pneumonitis, and enteritis). Tissue-invasive CMV disease is defined as CMV disease and CMV detected in tissue with histology, NAT or culture [15].

The link between cytomegalovirus (CMV) infection and the development of NODAT was first reported in 1985 in a renal transplant recipient [16]. Limited studies suggested that both asymptomatic CMV infection and CMV disease are independent risk factors for the development of NODAT. In a study consisting of 160 consecutive non-diabetic renal transplant recipients who were prospectively monitored for CMV infection during the first three months after transplantation, Hjelmesaeth and colleagues found that asymptomatic CMV infection was associated with a four-fold increased risk of new-onset diabetes (adjusted RR = 4.00; p = 0.025) [17]. Patients with active CMV infection had significantly lower median insulin release compared to their CMV negative counterparts, suggesting that the impaired pancreatic β

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

Table 1: ADA diagnostic criteria for diabetes mellitus.

***Corresponding author:** Dr. Matej Stančík, Clinic of Internal Medicine I, University Hospital Martin and Jessenius Faculty of Medicine, Comenius University, Slovak Republic. Tel: +421 43 4203 485; E-mail: matej_stancik@hotmail.com

Received May 25, 2016; **Accepted** June 13, 2016; **Published** June 20, 2016

Citation: Dedinská I, Stančík M, Laca Ľ, Miklušica J, Kantárová D, et al. (2016) Correlation between CMV Infection and NODAT. J Metabolic Synd 5: 205. doi:10.4172/2167-0943.1000205

cell insulin release may be involved in the pathogenic mechanism of CMV-associated NODAT. It is speculated that CMV-induced release of proinflammatory cytokines may lead to apoptosis and functional disturbances of pancreatic β-cells [18]. Randomized controlled trials have demonstrated that the incidence of CMV disease can be reduced by prophylaxis and preemptive therapies in solid-organ transplant recipients [19-21].

According to the recommendations of KDIGO, CMV chemoprophylaxis is indicated (except when donor and recipientboth have negative CMV serologies) by applying the oral ganciclovir or valganciclovir for the period of minimum 3 month after kidney transplantation and for the period of 6 weeks after the kidney transplantationin case of T-cell-depleting antibody therapy [15].

In our department, we apply chemoprophylaxis (valganciclovir) in case of seronegative recipient or seropositive donor (R+/D-) 100 days after transplantation. In case of applying antithymocyte globulin, we apply the prophylaxis for the period of 6 weeks. However, CMV viremia (by using the polymerase chain reaction – PCR) is monitored regularly in all recipients, except for R+/D-, as follows: the first 6 months after transplantation every 2 weeks, and from the 6^{th} – 12^{th} month after transplantation 1x per month.

Materials and Methods

In the retrospective analysis, we monitored CMV viremia as the risk factor for NODAT in the group of patients who underwent primary transplantation of kidney from a deceased donor in the Transplantation Center in Martin in the years 2009-2013. The patients with diabetes mellitus type 1 and 2 and the patients who had not finished 12 months from kidney transplantation were excluded from monitoring. The patients who had the mTOR inhibitor or cyclosporin A in their immunosuppresive regime were also excluded from monitoring because of prevent of results distortion by immunosuppression. In each patient, we recorded the age at the time of transplantation, sex, we identified recipients with risky HLA for NODAT and with polycystic kidney diseases, we recorded the number of HLA mismatches and the type of donor (ECD). In each patient, we identified CMV viremia (by PCR) as customary in our department: 2x per month during the first 6 months from kidney transplantation and 1x per month from the 6^{th}-12^{th} month after kidney transplantation. Retrospectively, we identified the patients who had a symptomatic CMV disease in the monitored period. The patients were divided into two sub-groups according to the development of NODAT in the monitored period – the control group and the NODAT group. NODAT was diagnosed in a standard way according to the ADA criteria. The groups were compared from the aspect of development of NODAT and CMV viremia during the entire monitored period, during the first 6 months after transplantation and the next following 6 months after transplantation, and we also compared CMV viremia in every month after kidney transplantation. In the end, we compared the function of the graft 1 year after kidney transplantation (by the estimate of glomerular filtration - eGFR by applying the CKD-EPI creat 2009 formula) and we compared the 12-month survival of the graft (censored for death) and the patients. By the correlation coefficient, we identified whether CMV viremia affects the function of the graft 12 months after kidney transplantation. All risk patients in the monitored group, i.e. the seronegative recipients who received the organ from a seropositive donor and the recipients who received the T-cell-depleting antibody were administered chemoprohylaxis. In case of a seronegative recipient, it was 100 days from kidney transplantation and in case of the T-cell-depleting antibody, it was 6 weeks from administration.

We used a certified statistical program MedCalc version 13. 1. 2. for statistical evaluation and we used the following statistical analyses: Student's t-test, chi-square test, correlation coefficient, Logistic regression, Cox proportional hazard model, Kaplan-Meier curves of survival. We consider the value $p < 0.05$ to be statistically significant.

Results

The group was composed of 167 patients, including 103 (61.7%) patients who were included in the control group and 64 (38.3%) patients in the group with development of NODAT in the monitored period. The average level of tacrolimus (during the monitored 12 months from kidney transplantation) was in both groups without any statistically significant difference (P = 0.5592), and similarly was the average dose of prednisone/day (P = 0.0877). The average dose of mycophenolate mofetil/dayor mycophenolate sodium was also without any statistically significant difference between the monitored groups (P = 0.0919 – mycophenolate mofetil and P = 0.1734 – mycophenolate sodium). In view of that, both groups were homogenous from the aspect of the applied immunosuppression, and the individual monitored parameters were not distorted by the applied immunosuppresion (Table 2). The characteristics of the group are given in Table 3. The patients in the NODAT group were significantly older than the patients in the control group, and during the monitored 12 months, the patients in the NODAT group received a statistically significant higher dose of methylprednisolone. However, in the multivariant analysis, the dose of methylprednisolone as an independent risk factor for NODAT was not identified (Table 4). Average methylprednisolone dose correlated with the incidence of acute rejection [r = 0.2614; 95 % CI for r = 0.06098-0.4416 (P = 0.0114)], but CMV replication was not linked to the average

	Control group n = 103	NODAT group n = 64	p value
Average level of TAC (ng/ml)	4.7 ± 0.9	4.8 ± 1.2	0.5592
Average dose of prednisone/day (mg)	8.2 ± 2.3	8.8 ± 2.0	0.0877
Average dose of MMF/day (mg)	849.4 ± 264.2	911.7 ± 175.4	0.0919
Average dose of mycophenolate sodium/day (mg)	670.7 ± 292	721.9 ±113	0.1734
TAC – Tacrolimus; MMF – Mycophenolate Mofetil			

Table 2: Comparison of the control group versus NODAT from the aspect of immunosuppression.

	Control group n = 103	NODAT group n = 64	p value
Age at the time of transplantation (years)	**43 ± 12.1**	**50.5 ± 9.6**	**<0.0001**
Males (%)	62.1	59.4	0.8627
HLA A30 (%)	2.9	0	0.4375
HLA B27 (%)	9.6	10.9	0.9937
HLA B42 (%)	1	0	0.8335
Average number of HLA mismatches	3.5 ± 1.2	3.7 ± 1.4	0.3266
APKD (%)	10.4	17.2	0.2839
ECD donor (%)	17.3	21.9	0.5926
Pulse therapy by methylprednisolone (%) except for induction	36.4	34.9	0.9792
average dose of (g) except for induction	**2.0 ± 0.7**	**2.3 ± 0.7**	**0.0086**
CMV replication (%)	45.8	45.2	0.9286
Average number of copies (cop/ml)	3500	3800	0.9763
DM2 – Diabetes Mellitus Type 2; APKD – Polycystic Kidney Disease; ECD – Extended Criteria Donor; CMV – Cytomegalovirus			

Table 3: Characteristics of the group – univariant analysis.

	Hazard ratio	CI 95 %	p value
Age at the time of transplantation < 30 years	0.3065	0.08262-1.1363	0.0769
Age at the time of transplantation 30-39 years	0.5000	0.0526-4.7518	0.5714
Age at the time of transplantation 40-49 years	0.7000	0.4292-1.1416	0.1529
Age at the time of transplantation 50-59 years	1.1376	1.0437-1.2399	0.0034
Age at the time of transplantation ≥ 60 years	2.5038	1.7179-3.6492	<0.0001
Pulse therapy by methylprednisolone (yes/no)	2.6024	0.7415-9.1334	0.1354
Average dose of (g) except for induction	1.1026	0.7115-1.7086	0.6622
DM2 – Diabetes Mellitus Type 2			

Table 4: Characteristics of the group– multivariant analysis.

methylprednisolone dose [r = 0.1633; 95 % CI for r = -0.0462-0.3542 (P = 0.1157)].

The average value of the CMV viremia (cop/ml) in the NODAT group and in the control group was without any statistically significant difference. We compared replication of CMV in the first 6 months after kidney transplantation with replication during the second half-year after transplantation, and we recorded in both groups significantly higher replication of CMV infection in the first half-year after transplantation. However, upon comparing the control group versus the NODAT group, no difference in replication in the first and in the second half-year after kidney transplantation was recorded (Figures 1-4).

CMV viremia in individual months after kidney transplantation is presented in Table 5. In the 10th month after kidney transplantation, we recorded significantly higher CMV viremia in the NODAT group, however, such difference was not confirmed in the multivariant analysis (Tables 5 and 6). In view of the foregoing, in our group, CMV is of no relevance to development of NODAT in the monitored periodin the first 12 months from kidney transplantation. We discovered that significantly more patients (70%) had diagnosed NODAT in the first 6 months after transplantation (P < 0.001) (Figure 5).

In the whole group, we identified the patients who developed the symptomatic form of CMV infection. In the whole group, it was only 6% patients. In the NODAT group, 10.9% patients had the symptomatic CMV infection, and in the control group it was 2.9% (0.0741).

The value of creatinine 12 months after transplantation was comparable in both groups, and also the eGFR (the limit of statistical significance) (Table 7). By the correlation coefficient we discovered that the higher number of copies CMV/ml worsens the function of the graft (characterized eGFR) 12 months after kidney transplantation (Figures 6 and 7).

Discussion

Many risk factors have been found to have influence on the development of NODAT. In 1985 Lehr et al. reported a case of cytomegalovirus (CMV) induced NODAT in a kidney recipient patient, after that the role of CMV infection in NODAT has been an area of interest to researchers [16]. Since then, other studies have supported [17,22] the relationship between them whilst other studies [23,24] have failed to prove this association. However, the influence of CMV infection on developing NODAT still remains a question. If the impact of CMV infection on higher incidence of NODAT is proven, initiating prophylaxis against CMV infection after transplantation will be strongly suggested [25]. In meta-analysis of authors Einollahi et al., it was discovered that the risk of NODAT in kidney transplants with CMV infection was 1.94 fold more as compared to individuals without CMV infection using adj ORs from the studies [26]. This significant relationship was proved by overall pooled OR using un-adj ORs. There was a difference in the result of evaluated studies in term of CMV induced NODAT. Though, three studies [27,28] reported no significant relationship between CMV infection and NODAT; other studies [17,23,29] detected CMV infection as the risk factor for NODAT. In

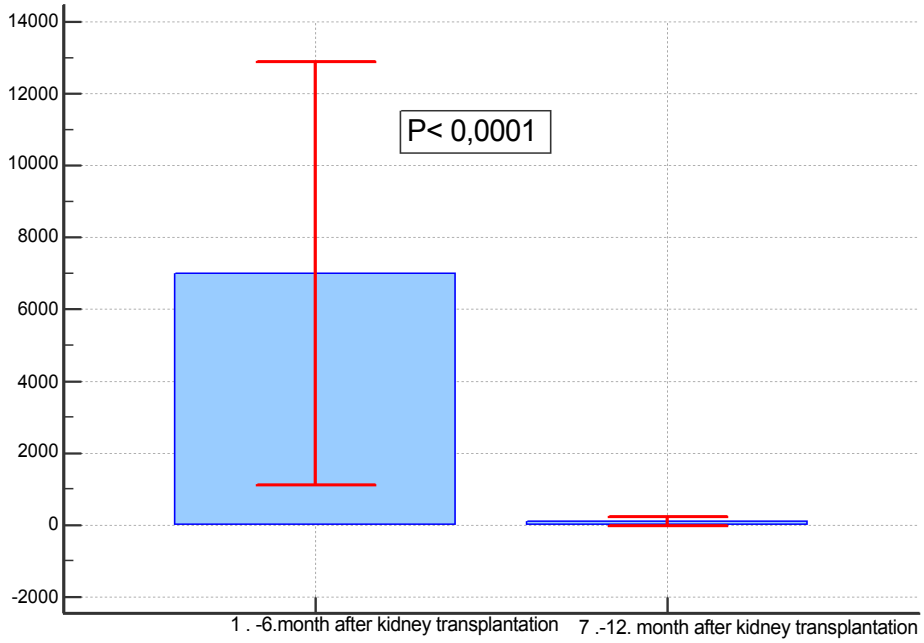

Figure 1: Replication of CMV 1st – 6th month versus 7th – 12th month after kidney transplantation – control group.

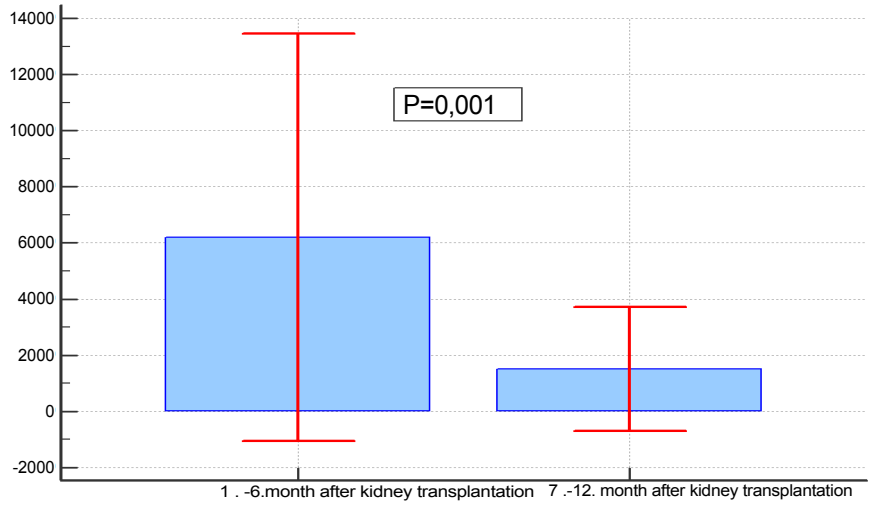

Figure 2: Replication of CMV 1st – 6th month versus 7th – 12th month after kidney transplantation – NODAT group.

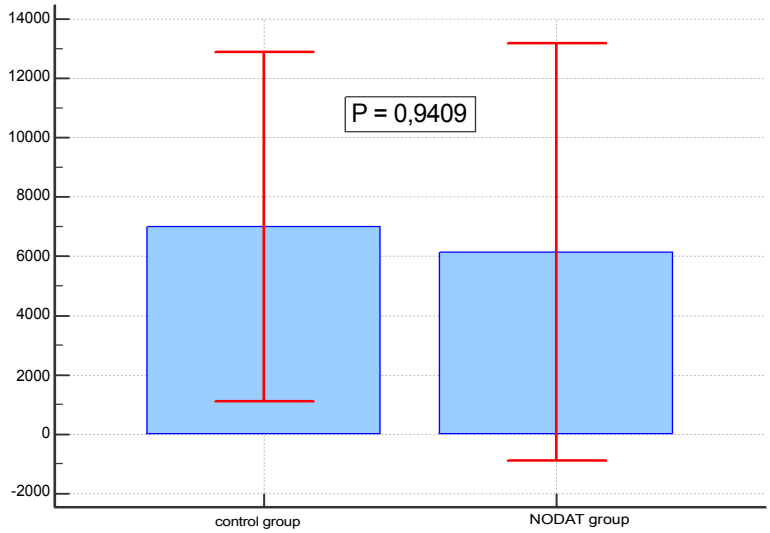

Figure 3: Replication of CMV 1st – 6th month after kidney transplantation: control group versus NODAT group.

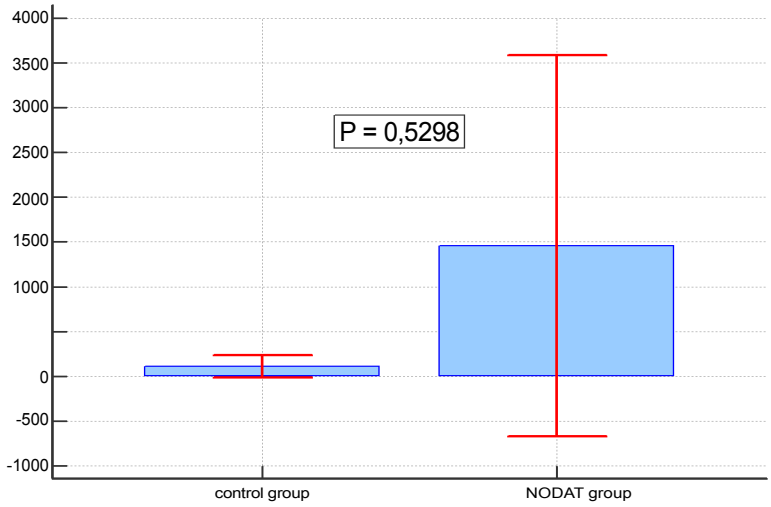

Figure 4: Replication of CMV 7th – 12th month after kidney transplantation: control group versus NODAT group.

Months after transplantation	control group (n=103) CMV PCR (cop/ml)	NODAT group (n=64) CMV PCR (cop/ml)	p value
1	1177.1	0	0.3568
2	6489.6	24241.9	0.3281
3	26346	4975.8	0.3080
4	4578.9	6770.9	0.6551
5	659.4	601.6	0.9007
6	2729.2	270.9	0.2195
7	52.1	2233.9	0.2138
8	338.5	250	0.8397
9	0	41.9	0.0858
10	**104.2**	**48256.6**	**<0.0001**
11	177.1	16.1	0.4674
12	0	48.4	0.4382

Table 5: CMV replication – individual months after kidney transplantation (univariant analysis).

Months after transplantation	Odds ratio	95% CI	p value
1	0.9990	0.6843-1.4582	0.9957
2	1.0000	1.0000-1.0000	0.5884
3	1.0000	1.0000-1.0000	0.1969
4	1.0000	1.0000-1.0000	0.8043
5	1.0001	0.9999-1.0003	0.3769
6	0.9999	0.9998-1.0001	0.3515
7	1.0000	0.9999-1.0001	0.5512
8	0.9999	0.9994-1.0003	0.6266
9	1.0210	0.0000-24969.8938	0.9968
10	1.0000	1.0000-1.0001	0.6025
11	0.9989	0.3234-3.0852	0.9985
12	1.0066	0.0031-328.3802	0.9982

Table 6: CMV replication – individual months after kidney transplantation (multivariant analysis).

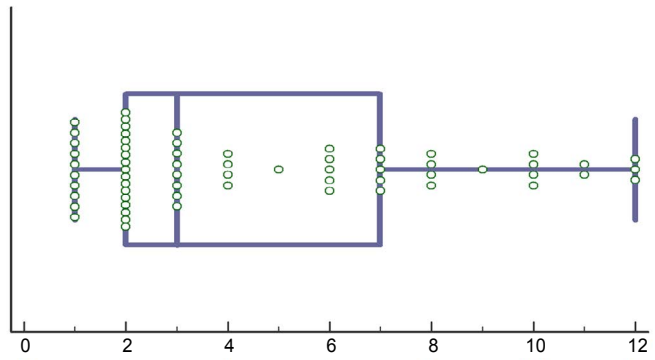

Figure 5: Time of diagnostics of NODAT (months after transplantation).

addition, Valderhaug et al. [30] only found the relationship between CMV infection and NODAT in univariate analysis whilst a multivariate analysis, adjusted for age, prednisolone, type of cohort, HLA-B27 phenotype and BMI did not support this association.

According to the above mentioned metaanalysis of the authors Einollahi et al., the studies used different criteria to identify CMV infection. Isolation of the CMV virus and detection of viral proteins or nucleic acid are different ways to recognize CMV infection [27]. In addition, active systemic CMV infection can be diagnosed as CMV-DNA in plasma by polymerase chain reaction methods or by detection of CMV-antigenemia in leucocytes (i.e., CMVpp65) (18). Four from seven works in analysis did not report a criterion for identifying CMV infection [22,27-29]. Three remaining studies used different criterion to recognize CMV infection; Hjelmesaeth et al. [17] defined CMV infection as one or more CMV pp65 antigen-positive cells per 100.000 leucocytes, Marin et al. [24] defined it as more than 50 infected cells per 200,000 leucocytes using the pp65 assay or isolation of CMV antigenemia or fourfold increase in the baseline IgG and Valderhaug et al. [30] diagnosed it by CMV-pp65 antigen in leucocytes or CMV-DNA in plasma, but they did not report any details. Thus using various criteria and methods with different sensitivity and specificity can lead to an overestimate or may in fact underestimate CMV infection in the studies. The studies which determine CMV viremia by PCR may expain the relationship between CMV and NODAT.

In our group, we had not detected any relationship between replication of CMV and development of NODAT. The group was homogenous from the aspect of immunosuppresion. The results of our analysis and the low occurrence of symptomatic CMV infection is, in our opinion, related to the intensive monitoring of CMV viremia (PCR) after transplantation (the first 6 months, CMV viremiais determined every 1 month, in the second half-year every 6 weeks). In the risk patients (seronegative donor and seropositive recipient), we monitor CMV viremia also in the second year after transplantation, every 2 months. The patients who were treated by T-cell-depleting antibody, have in our center monitored CMV viremia every 1 month for 3 months after the end of therapy. All recipients with the increased risk of CMV infection were administered chemoprophylaxis according to the KDIGO recommendations of 2009 [15].

Prospective observational cohort study of authors Smedbråten et al. is an extension of the previous study reporting effects of cytomegalovirus (CMV) on the graft and patient survival in 471 patients who underwent kidney transplantation between 1994 and 1997. None of the patients received CMV prophylaxis or preemptive treatment. CMV infection was an independent significant risk factor for mortality in multivariate analysis (HR = 1.453, 95% CI 1.033–2.045, p = 0.032) [31]. This observed association between CMV infection and long-term graft and patient outcome may be altered by prophylaxis or preemptive CMV therapy. In a study by Kliem et al., oral ganciclovir prophylaxis was compared to intravenous preemptive CMV therapy [32]. Compared to preemptive therapy, prophylaxis was found to be significantly associated with improved long-term (4 yr) uncensored graft survival, with the greatest benefit observed in the donor +/recipient + CMV serostatus group. Moreover, when analyzing the death-censored graft survival, prophylaxis significantly improved graft survival in the donor +/recipient + CMV serostatus group. Opelz et al. reported from analyses of register data that CMV prophylaxis was significantly associated with improved graft survival both censored and uncensored for death; but in both cases only in the donor +/recipient – CMV serostatus group [33]. In our group, we identified relationship between CMV viremia and function of the graft 12 months after kidney transplantation. With the increasing number of CMV copies/ml, eGFR is worsened one year after kidney transplantation.

CMV replication after transplantation may contribute to reduced graft function and survival through the associated inflammation and

	Control group n = 103	NODAT group n = 64	p value
Creatinine 12 months after transplantation (μmol/l)	139.4 ± 38.1	140.1 ± 43.6	0.9144
eGFR 12 months after transplantation (ml/min)	51 ± 14.4	46.8 ± 13.2	0.0635

Table 7: Comparison of function of the graft (creatinine and eGFR) 12 months after transplantation.

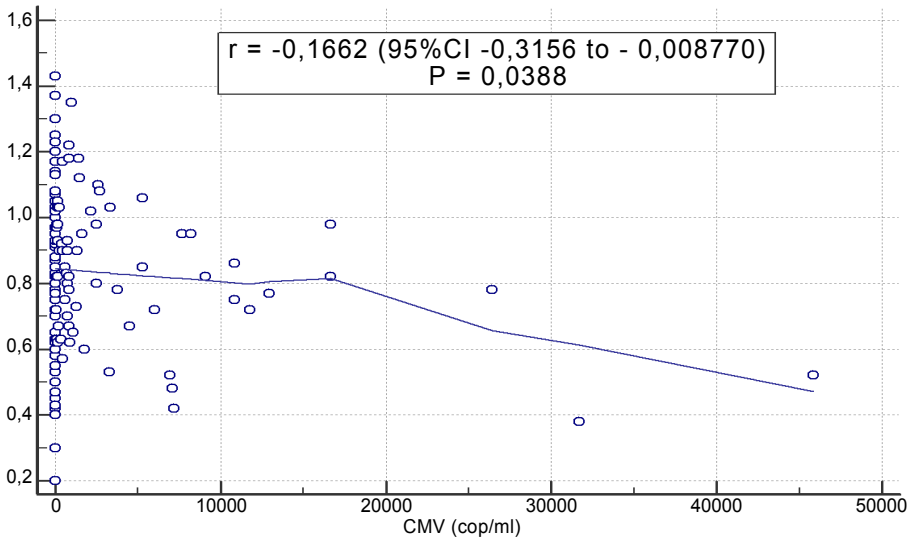

Figure 6: Correlation between CMV and eGFR (CKD-EPI) 12 months after kidney transplantation.

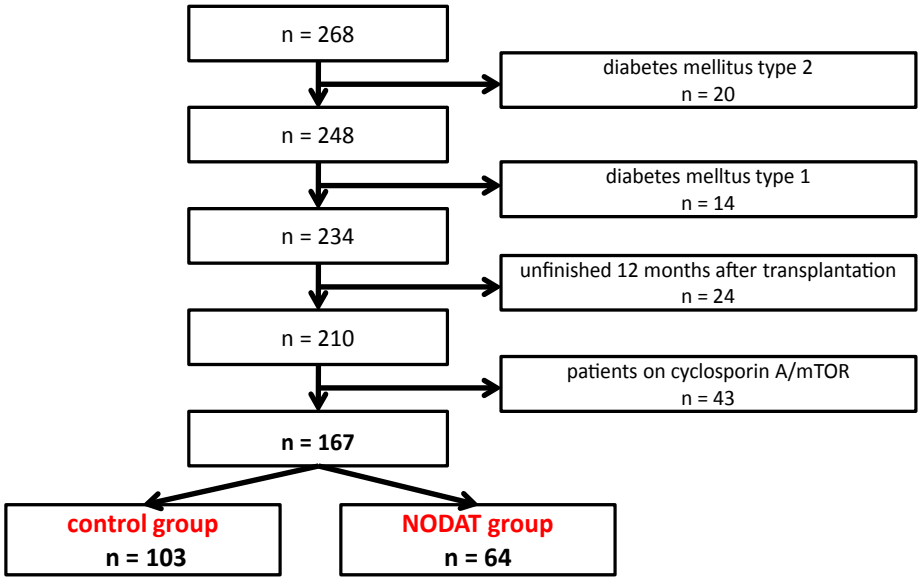

Figure 7: Selection of patients for the analysis.

cytokine release [34]. Uncontrolled replication of CMV triggers direct and/or indirect effect in transplant recipients [35]. When CMV is reactivated under immunosuppressive conditions, it has both direct effects, such as development of CMV disease, and indirect effects on transplantation, including increased incidence of allograft rejection [36].

In our study, survival of the patients (censored for death) as well as survival of the graft is numerically worse in the NODAT group, no statistically significant difference was confirmed. We assume that the survival of patients with NODAT is significantly worse from the long-term aspect (10 and more years). Intensive monitoring of glycaemia and early diagnostics and treatment of NODAT, as well as check-up of the other affectable risk factors for NODAT are able to significantly improve survival of both the patients and the graft and to decrease the cardiovascular mortality and morbidity.

Conclusion

Our analysis suggests that by regular monitoring of CMV viremia and applying chemoprophylaxis for risk recipients (in our case, seropositive donor/seronegative recipient or recipient after T-cell-depleting antibody therapy) is not the CMV risk factor for NODAT. The results of the analysis (or CMV viremia or development of NODAT) are not distorted by the administered immunosuppressive treatment – from the aspect of immunosuppression, the group was homogenous. Regular monitoring of CMV viremia and chemoprophylaxis may affect not only development of NODAT, but it is possible (as in our group) to eliminate the number of patients with symptomatic CMV infection. Frequent monitoring of CMV viremia may increase the costs on care about the recipient after kidney transplantation, however, we eventually decrease the costs on treatment of later complications arising from CMV infection. In the patients after kidney

transplantation, the most important risk factor for NODAT is the age at the time of transplantation (more than 50 years of age), prediabetes before transplantation, positive family history of diabetes mellitus type 2, and the body mass index of more than 30 kg/sqm at the time of transplantation. Regular weight and waist circumference control in patients after kidney transplantation leads to identification of risk patients for NODAT. Screening of risk factors for diabetes mellitus should be done even before placing the patient on the waiting list and it is advisable to carry out the oral glucose tolerance test (oGTT) also in patients with physiological levels of fasting glycemia [37,38].

Funding

This paper was supported by VEGA grant 1/0160/16 Diagnostic - prognostic relevance of adipocytokine network and glucose homeostasis assessment in cachexia.

References

1. Hjelmesaeth J, Hartmann A, Leivestad T, Holdaas H, Sagedal S, et al. (2006) The impact of early-diagnosed new-onset post-transplantation diabetes mellitus on survival and major cardiac events. Kidney Int 69: 588-595.
2. Bee YM, Tan HC, Tay TL, Kee TY, Goh SY, et al. (2011) Incidence and risk factors for development of new-onset diabetes after kidney transplantation. Ann Acad Med Singapore 40: 160-167.
3. Cosio FG, Pesavento TE, Kim S, Osei K, Henry M, et al. (2002) Patient survival after renal transplantation: IV. Impact of post-transplant diabetes. Kidney Int 62: 1440-1446.
4. Pham PT, Pham PM, Pham SV, Pham PA, Pham PC (2011) New onset diabetes after transplantation (NODAT): an overview. Diabetes Metab Syndr Obes 4: 175-186.
5. Davidson J, Wilkinson A, Dantal J, Dotta F, Haller H, et al. (2003) New-onset diabetes after transplantation: 2003 International consensus guidelines. Proceedings of an international expert panel meeting. Barcelona, Spain, 19 February 2003. Transplantation 75: SS3-24.
6. Wilkinson A, Davidson J, Dotta F, Home PD, Keown P, et al. (2005) Guidelines for the treatment and management of new-onset diabetes after transplantation. Clin Transplant 19: 291-298.
7. Montori VM, Basu A, Erwin PJ, Velosa JA, Gabriel SE, et al. (2002) Posttransplantation diabetes: a systematic review of the literature. Diabetes Care 25: 583-592.
8. Rubin RH (1993) Infectious disease complications of renal transplantation. Kidney Int 44: 221-236.
9. Farrugia E, Schwab TR (1992) Management and prevention of cytomegalovirus infection after renal transplantation. Mayo Clin Proc 67: 879-890.
10. Brennan DC (2001) Cytomegalovirus in renal transplantation. J Am Soc Nephrol 12: 848-855.
11. Smith SR, Butterly DW, Alexander BD, Greenberg A (2001) Viral infections after renal transplantation. Am J Kidney Dis 37: 659-676.
12. Kotton CN, Fishman JA (2005) Viral infection in the renal transplant recipient. J Am Soc Nephrol 16: 1758-1774.
13. Büchler M, Hurault de Ligny B, Madec C, Lebranchu Y (2003) Induction therapy by anti-thymocyte globulin (rabbit) in renal transplantation: a 1-yr follow-up of safety and efficacy. Clin Transplant 17: 539-545.
14. Burke GW 3rd, Kaufman DB, Millis JM, Gaber AO, Johnson CP, et al. (2004) Prospective, randomized trial of the effect of antibody induction in simultaneous pancreas and kidney transplantation: three-year results. Transplantation 77: 1269-1275.
15. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group (2009) KDIGO clinical practice guideline for the care of kidney transplant recipients. Am J Transplant 9: S1-155.
16. Lehr H, Jao S, Waltzer WC, Anaise D, Rapaport FT (1985) Cytomegalovirus-induced diabetes mellitus in a renal allograft recipient. Transplant Proc 17: 2152-2154.
17. Hjelmesaeth J, Sagedal S, Hartmann A, Rollag H, Egeland T, et al. (2004) Asymptomatic cytomegalovirus infection is associated with increased risk for new-onset diabetes and impaired insulin release after renal transplantation. Diabetologia 47: 1550-1556.
18. Hjelmesaeth J, Muller F, Jenssen T, Rollag H, Sagedal S, et al. (2005) Is there a link between cytomegalovirus infection and new-onset posttransplantation diabetes mellitus? Potential mechanisms of virus induced β-cell damage. Nephrol Dial Transplant 20: 2311-2315.
19. Hodson EM, Craig JC, Strippoli GF, Webster AC (2008) Antiviral medications for preventing cytomegalovirus disease in solid organ transplant recipients. Cochrane Database Syst Rev.
20. Hodson EM, Jones CA, Strippoli GF, Webster AC, Craig JC (2007) Immunoglobulins, vaccines or interferon for preventing cytomegalovirus disease in solid organ transplant recipients. Cochrane Database Syst Rev: CD005129.
21. Strippoli GF, Hodson EM, Jones C, Craig JC (2006) Preemptive treatment for cytomegalovirus viremia to prevent cytomegalovirus disease in solid organ transplant recipients. Transplantation 81: 139-145.
22. Hjelmesaeth J, Hartmann A, Kofstad J, Stenstrøm J, Leivestad T, et al. (1997) Glucose intolerance after renal transplantation depends upon prednisolone dose and recipient age. Transplantation 64: 979-983.
23. Sulanc E, Lane JT, Puumala SE, Groggel GC, Wrenshall LE, et al. (2005) New-onset diabetes after kidney transplantation: an application of 2003 International Guidelines. Transplantation 80: 945-952.
24. Marin M, Renoult E, Bondor CI, Kessler M (2005) Factors influencing the onset of diabetes mellitus after kidney transplantation: a single French center experience. Transplant Proc 37: 1851-1856.
25. Nemati E, Taheri S, Pourfarziani V, Einollahi B (2008) Cytomegalovirus disease in renal transplant recipients: an Iranian experience. Exp Clin Transplant 6: 132-136.
26. Einollahi B, Motalebi M, Salesi M, Ebrahimi M, Taghipour M (2014) The impact of cytomegalovirus infection on new-onset diabetes mellitus after kidney transplantation: a review on current findings. J Nephropathol 3: 139-148.
27. Madziarska K, Weyde W, Krajewska M, Patrzalek D, Janczak D, et al. (2011) The increased risk of post-transplant diabetes mellitus in peritoneal dialysis-treated kidney allograft recipients. Nephrol Dial Transplant 26: 1396-1401.
28. Numakura K, Satoh S, Tsuchiya N, Horikawa Y, Inoue T, et al. (2005) Clinical and genetic risk factors for posttransplant diabetes mellitus in adult renal transplant recipients treated with tacrolimus. Transplantation 80: 1419-1424.
29. Yang WC, Chen YS, Hsieh WC, Shih MH, Lee MC (2006) Post-transplant Diabetes Mellitus in Renal Transplant Recipients-Experience in Buddhist Tzu Chi General Hospital. Tzu Chi Med J 18: 185-191.
30. Valderhaug TG, Hjelmesaeth J, Rollag H, Leivestad T, Røislien J, et al. (2007) Reduced incidence of new-onset posttransplantation diabetes mellitus during the last decade. Transplantation 84: 1125-1130.
31. Smedbråten YV, Sagedal S, Leivestad T, Mjøen G, Osnes K, et al. (2014) The impact of early cytomegalovirus infection after kidney transplantation on long-term graft and patient survival. Clin Transplant 28: 120-126.
32. Kliem V, Fricke L, Wollbrink T, Burg M, Radermacher J, et al. (2008) Improvement in long-term renal graft survival due to CMV prophylaxis with oral ganciclovir: results of a randomized clinical trial. Am J Transplant 8: 975-983.
33. Opelz G, Döhler B, Ruhenstroth A (2004) Cytomegalovirus prophylaxis and graft outcome in solid organ transplantation: a collaborative transplant study report. Am J Transplant 4: 928-936.
34. Helanterä I, Loginov R, Koskinen P, Törnroth T, Grönhagen-Riska C, et al. (2005) Persistent cytomegalovirus infection is associated with increased expression of TGF-beta1. PDGF-AA and ICAM-1 and arterial intimal thickening in kidney allografts. Nephrol Dial Transplant 20: 790-796.
35. Helanterä I, Egli A, Koskinen P, Lautenschlager I, Hirsch HH (2010) Viral impact on long-term kidney graft function. Infect Dis Clin North Am 24: 339-371.
36. Ishibashi K, Tokumoto T, Shirakawa H, Oguro T, Yanagida T, et al. (2014) The presence of antibodies against the AD2 epitope of cytomegalovirus glycoprotein B is associated with acute rejection after renal transplantation. Microbiol Immunol 58: 72-75.
37. Zilinska Z, Chrastina M, Trebaticky B, Breza J Jr, Slobodnik L, et al. (2010) Vascular complications after renal transplantation. Bratisl Lek Listy 111: 586-589.
38. Dedinská I, Laca Ľ, Miklušica J, Rosenberger J, Žilinská Z, et al. (2015) Waist circumference as an independent risk factor for NODAT. Ann Transplant 20: 154-159.