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Assessment of Serum Soluble CD30 Levels in Pediatric Kidney Transplant Recipients

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Abstract

BACKGROUND: CD30 is considered to be a marker for the activated immune system; however, its association with acute rejection and kidney graft function showed severe heterogeneity.

AIM: The aim of this study is to examine the predictive value of soluble CD30 (sCD30) levels for kidney transplantation (KT) outcomes in children.

MATERIALS AND METHODS: CD30 in serum was measured by ELISA technique in 50 pediatric kidney transplant recipients (KTRs) within 13.4 ± 4.5 days before and within 19.5 ± 9.2 days after KT. sCD30 values were correlated with clinical, laboratory, and immunosuppressive (IS) therapy data and graft function of included patients. Twenty age/gender-matched healthy controls participated as reference values for sCD30 levels.

RESULTS: Our study revealed that serum levels of CD30 showed a significant relation between serum sCD30 levels: Pre/post-transplantation ($p = 0.02$) with increasing sCD30 levels after transplantation (71.60 pg/mL vs. 90.20 pg/mL). In the time, there were no relations between sCD30 with other parameters.

CONCLUSIONS: Our results suggest that the measurement of serums CD30 levels may be used as a valuable biomarker in renal transplantation when it is measured pre/post-transplantation.

Introduction

Antibody-mediated rejection (AMR) is the most common cause of allograft failure in kidney transplant recipients (KTRs) [1]. Serum creatinine and proteinuria reflect kidney allograft function, but they are non-specific tools. Despite its limitations (being invasive procedure with increased risk of bleeding and infection), kidney graft biopsy remains the gold standard method for confirming AMR [2]. This makes developing non-invasive biomarkers that identify KTRs at higher risk of immunological-mediated allograft loss mandatory [3].

Soluble CD30 (sCD30) is a member of the tumor necrosis factor/nerve growth factor receptor superfamily with a molecular weight of 120-kDa. It is expressed on natural killer cells, dendritic cells, regulatory T cells, as well as CD4+ and CD8+ activated T cells but not on resting T cells and it is considered to be a marker for activated immune system in which T cells can damage the allograft [4].

Although the function of CD30 remains unclear, there is limited knowledge of CD30 expression in various subtypes of post-transplant lymphoproliferative disorder and its correlation to clinicopathological features [5].

Many investigators have shown that higher pre-transplant sCD30 is an indicator for the risk of acute kidney graft rejection [6], while other authors did not find such an association [7].

Beside its expression on activated T cells, sCD30 is also expressed on activated B cells. It was found that sCD30 correlates with disease activity in patients with autoimmune diseases such as systemic lupus erythematosus, granulomatosis with polyangiitis, and rheumatoid arthritis [8]. On the other hand, sCD30 was approved for the treatment of relapsed or refractory Hodgkin lymphoma and anaplastic large cell lymphoma [9].

The heterogeneity of published data regarding the association between sCD30 and graft rejection or loss makes further investigation of the immunological role of sCD30 in kidney transplantation (KT) is crucial. In this study, we were in the process of determining the significance of sCD30 as indicator of graft functions and graft outcomes in pediatric KTRs.

Materials and Methods

Patients

This is a cross-sectional case–control study that included 50 consecutive pediatric KTRs. All included patients received their kidney transplant from living donor according to national regulations and were following up at KT Outpatient Clinic, Cairo University Children Hospital (CUCH), Cairo, Egypt. The study was conducted over 18 months between June 2018 and December 2019.

Included patients had stable graft function (defined as serum creatinine <1 mg/dL) with no decline in GFR within the past 3–6 months, with no proteinuria (spot urine protein–creatinine ratio <200 mg/g). Blood pressure (BP) was evaluated according to the American Academy of Pediatrics; 32 (64%) patients had elevated BP (≥90th percentile to <95th percentile or 120/80 mm Hg to <95th percentile (whichever is lower) and 18 (36%) patients with normal BP (<90th percentile) before KT. After KT, 38 (76%) patients had their BP controlled (<90th percentile) on double antihypertensive drugs upon post-operative hospital discharge; then, antihypertensive medications were discontinued over the next 1–2 months.

All patients were recipients for their first kidney graft except for one (2%) patient who received a previous transplant. All the donors had no medical problem apart from anemia and controlled HTN. All KTRs were vaccinated against HBV. Subjects were not routinely screened for the development of the novel human leukocyte antigens (HLA) antibodies post-transplant. Anatomical problems were excluded by ultrasound and nuclear scans. KTRs showing signs of ureteral obstruction and/or renal artery stenosis of the graft, arterial, venous thrombosis, and infection-induced fever were excluded from the study.

All patients underwent pre-transplantation hemodialysis for a median duration of 12 months. Each HD session was for 4 h, 3 times per week using polysulfone membranes and bicarbonate dialysate using a blood flow rate of 80–150 mL/min and a dialysate flow rate of 500 mL/min. The dialysate fluids were prepared from concentrated salt solutions and from bicarbonate powder in sealed containers [10].

Twelve healthy children with age-body mass index and gender matched with no clinical signs or family histories of renal disease were included as controls. They were recruited from the Pediatric Clinic of Centre of Excellence© of the National Research Centre (NRC) (CENRC).

Ethical issues

The study was approved by the ethical committees of the NRC and Pediatric Nephrology Unit, CUCH, Egypt. Blood samples from patients and control were collected upon written informed consent in accordance with the declaration of Helsinki [11].

IS regimens

Antibody induction therapy (either IL-2 receptor blocking antibody [anti-IL-2R Ab, basiliximab] or antithymocyte globulin [ATG]) was received by 46 patients, while 4 patients did not receive antibody induction immunosuppression.

All children received intravenous methylprednisolone perioperative, as a part of induction immunosuppression. Steroids were tapered to oral form a week after KT then kept on high dose till the end of the 1st month. By the 1st year of KT, steroids gradually withdrawn to oral low-dose prednisolone.

In addition to steroids, IS protocol included calcineurin inhibitor (CNI) and mycophenolate mofetil (MMF). MMF was administrated as an adjuvant therapy to all patients for at least 1-month post-transplantation then continued in 46 patients afterward and replaced by everolimus (mammalian target of rapamycin inhibitors [mTORI]), with low CNI dose in 4 patients. The initial dose of MMF was 360–1440 mg/day, and the dose was modified based on adverse effects such as diarrhea or leukopenia.

Clinical parameters

The potential factors which may affect serum sCD30 levels were included. The number of HLA mismatch (out of 6 HLA alleles for the 3 assessed HLA classes; HLA class A, HLA class B, HLA class DR), donor relation (related versus unrelated), episode of cytomegalovirus (CMV) infection, graft function (in term of serum creatinine and calculated estimated glomerular filtration rate), and CNI trough levels at assessment were evaluated.

Cold ischemia time was defined as the time elapsed between clamping of the donor graft artery and de-clamping of the anastomosing vessel in the recipient (signifies the duration of ischemia/reperfusion injury). Acute rejection (AR) was defined as a rise in serum creatinine of 20%–30% from baseline levels and accompanied by clinical symptoms and signs as fever, graft tenderness, and oliguria usually within days to weeks after the transplant [12]. Presumed acute rejection (PRAR) was defined as an episode of AR, which is diagnosed clinically and treated by pulse methylprednisolone; however, a biopsy the sample was not taken or did not have the signs of rejection according to the Banff criteria. Biopsy-proven acute rejection (BPAR) was defined as acute graft dysfunction accompanied by pathological evidence of rejection [13].

Chronic allograft dysfunction (CAD) was defined clinically as a progressive decline of graft function with ≥15% irreversible increase in creatinine level within 1–3 months and proteinuria ≥1 g/24 h accompanied with a pathological diagnosis of interstitial fibrosis and tubular atrophy [14].

Serum sCD30 assay

Peripheral blood samples were obtained in healthy controls (HCs) and KTRs. Blood samples were withdrawn within (13.4 ± 4.5) days before and within (19.5 ± 9.2) days after transplantation in KTRs. The samples were analyzed for sCD30 using a commercially available, enzyme-linked immunoassay ELISA kit (Bender MedSystems GmbH, Wien, Austria) in accordance with the manufacturer's instructions. The absorbance of microwells was measured at 450 nm. The concentration of sCD30 was determined by comparing the optical density of sample wells with the optical density of wells with standard dilutions of sCD30.

Statistical analysis

Statistical analysis of data was done using SPSS version 25.0. Chi-square test was used for comparison between data presented as frequency and percentage. The student *t*-test was used for comparison between data presented as median. Analysis of variance *post hoc* test was used for multiple comparisons. Correlation between various variables was done using Spearman's rank correlation equation. Sample size was measured to be 45 or more to have a confidence level of 95% that the real value is within ±5% of the measured/surveyed value with a calculated power of the study about 80% [15]. $p < 0.05$ was considered as statistically significant.

Results

Demographics, clinical, and laboratory parameters of KTRs and HCs are summarized in Table 1. The original renal disease of KTRs was obstructive uropathy in 18 patients (36%), inherited nephropathy in 14 patients (28%), unknown in 14 patients (28%), and chronic glomerulopathy in 4 patients (8%). As for consanguineous marriage between the father and mother of patients, we found that 74% of our patients from non-consanguineous marriage. By taking the family history, we found that two of the patients had a brother who suffered from kidney problems and had a kidney transplant.

The median of sCD30 levels in KTRs and HCs was 90.20 pg/mL and 146.80 pg/mL, respectively (p = 0.27). No significant correlations were detected between sCD30 and other laboratory parameters.

As illustrated in Table 2, pre-transplant serum level of sCD30 in KTRs showed a significant relation with its levels after KT with increasing sCD30 level after transplantation (Median 71.60 pg/mL vs. 90.20 pg/ml, p = 0.02) (Figures 1 and 2). Donor relations did not show a significant association with sCD30 (levels in related (62.60 pg/mL) versus non-related donor KTRs (117.30 pg/mL). As such, other subgrouping of KTRs according to their CMV status, immunosuppression medications, AR episodes (either PRAR or BPAR) did not show significant association with sCD30. No significant difference was found in sCD30 on comparing patients with CAD versus patients with no CAD (89.60 pg/mL and 94.40 pg/mL, respectively, p = 0.40).

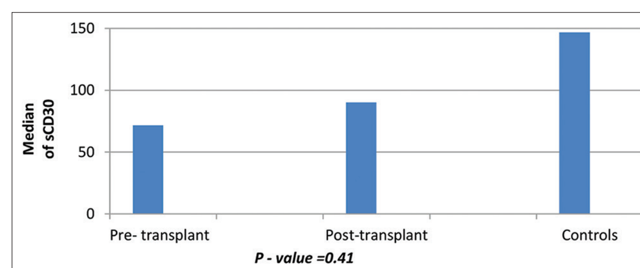

Figure 1: Median values of serum sCD30 levels in different groups; pre-transplant, post-transplant and controls groups and by analysis of variance p = 0.41, in time by spearman, pre-transplant versus post-transplant p = 0.02, pre-transplant versus controls p = 0.59, post-transplant versus controls p = 0.2, p < 0.05 was considered significant

No significant difference was found in sCD30 in different antibody induction therapy groups (ATG group:

Table 1: The demographics clinical and laboratory data of the cases and controls (sCD30 comparing by the median)

Data	KTRs (n = 50)	Controls (n = 12)	p-value	CD30 p- value	CD30 Correlation Coefficient
Age at assessment (years)	12.94 ± 4.23	10.70 ± 4.51	0.13	0.27	−0.16
Sex (male/female)	35/15 (70%/30%)	8/4 (66.7%/33.3%)	0.12		
Pre-transplantation FU duration (days)	13.4 ± 4.5			0.60	−0.07
Post-transplantation FU duration (days)	19.5 ± 9.2			0.22	0.17
Dialysis duration (months)	21.70 ± 25.34			0.53	0.09
BMI (kg/m^2)	22.63 ± 7.88	23.60 ± 8.44	0.859	0.53	−0.09
SBP (mmHg)	109.40 ± 10.5	95.54 ± 9.70	0.0001	0.82	−0.03
DBP (mmHg)	70.40 ± 8.91	61.55 ± 10.10	0.0001	0.99	0.00
Donor Age (years)	37.18 ± 6.21			0.34	−0.14
Tx weight (kg)	26.25 ± 9.53			0.21	−0.18
Cold ischemia time (min)	52.45 ± 12.30			0.79	0.04
PRD initial dose (mg/day)	184.00 ± 55.73			0.21	−0.18
PRD at 12 mo (mg/day)	4.23 ± 1.55			0.94	0.01
Trough cyclosporine level (ng/mL)	110.83 ± 18.55			0.19	−0.18
Trough tacrolimus (ng/mL)	6.26 ± 1.16			0.78	−0.04
BUN (mg/dL)	19.78 ± 11.69			0.89	0.02
Serum creatinine (mg/dL)	0.9 ± 0.3	0.9 ± 0.17	0.14	0.38	−0.17
eGFR (mL/min/1.73 m^2)	76.20 ± 22.10	96 ± 18.8	0.0203	0.94	−0.01
Hb (gm/dL)	10.84 ± 1.17	14.23 ± 1.50	<0.0001	0.95	0.01
TLC [$\times 10^3$/mm-^{3}]	7.83 ± 2.61	3.57 ± 1.42	<0.0001	0.67	0.06
PLT [$\times 10^3$/mm-^{3}]	223.06 ± 78.41	269.45 ± 84.02	0.0057	0.71	0.05
CD30	382.92 ± 1027.36 (90.20)	348.84 ± 386.50 (146.80)	0.27		0.35
CD4%	34.32 ± 9.58	34.78 ± 10.01	0.882	0.24	−0.17

Data were represented mean ± standard deviation, frequency, and percentage or median as applicable. KT: Kidney transplantation, FU: Follow-up, BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, HB: Hemoglobin, eGFR: Estimated glomerular filtration rate, Tx: Transplantation, PRD: Prednisolone, BUN: Blood urea nitrogen, TLC: Total leucocyte count, PLT: Platelet count. p<0.05 was considered significant

Table 2: Comparisons of sCD30 levels in the different subgroups of transplanted patients (n = 50)

Subgroups	Median	p-value
Gender variation		
Male = 35	90.80	0.24
Female = 15	59.60	
Donor relation		
Related donor (n = 38)	62.60	0.18
Non-related donors (n = 12)	117.80	
Pre- and post-transplantation		
Pre-transplantation	71.60	0.02
Post-transplantation	90.20	
Number of mismatch		
Mismatch = 1	69.20	0.46
Mismatch >1	92.60	
Antibody induction therapy		
ATG (n = 34)	80.60	0.80
Basiliximab (n = 12)	115.40	
No antibody induction (n = 4)	90.20	
Immunosuppression protocol		
CsA based protocol (n = 14)	106.40	0.85
Tacrolimus-based protocol (n = 32)	90.80	
m-TORI low CsA protocol (n = 4)	17.05	
CNI used		
Tacrolimus (n = 17)	90.20	0.64
CsA (n = 33)	89.60	
CMV status		
CMV IG g+ve (n = 44)	90.20	0.65
CMV IG g−ve (n = 6)	124.20	
Previous PRAR episodes		
No PRAR (n = 16)	65.60	0.71
Yes PRAR (n = 34)	92.60	
Previous BPAR episodes		
No BPAR (n = 36)	90.80	0.34
Yes BPAR (n = 14)	87.20	
Pathological evidence of CAD		
No CAD (n = 43)	94.40	0.40
Yes CAD (n = 7)	89.60	
AMR		
No AMR (no = 49)	89.60	0.76
Yes AMR (no = 1)	4988.00	

Data were represented mean ± standard deviation, frequency, and percentage or median as applicable. KTRs: Kidney transplantation recipients, HD: Hemodialysis, ATG: Antithymocyte globulin, IS: Immunosuppression, CNI: Calcineurin inhibitor, CsA: Cyclosporine, mTORI: Mammalian target of rapamycin inhibitors, CMV: Cytomegalovirus, PRAR: Presumed acute rejection, BPAR: Biopsy-proven acute rejection. CAD: Chronic allograft dysfunction, AMR: Antibody-mediated rejection). p<0.05 was considered significant

80.60 vs. basiliximab group: 115.40 vs. no antibody induction group: 90.20).

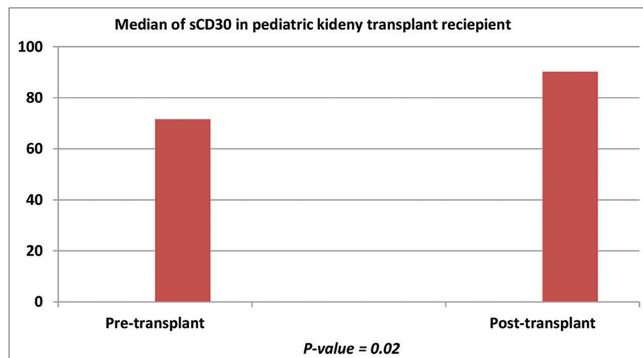

Figure 2: Median values of serum sCD30 levels in pre-transplant and post-transplant groups. p = 0.02. p < 0.05 was considered significant

Discussion

Expressional markers for the activated immune system are important topics of study in KT, in which activated T cells – which increase in the process of transplantation – can damage the allograft. Therefore, those markers are potential indicators of graft functions that could carry the hope of replacing the need for invasive biopsies. sCD30 is different from the rest of other markers for graft functions in KT. Researches differed in its importance as well as in the timing of its measurement in relation to transplantation.

In 2002, Pelzl *et al*. first indicated that only measurement of sCD30 levels before transplantation determined graft functions [16]. Researches were carried out confirming their results about pre-transplant sCD30 levels [17], [18]. However, several following studies confirmed that not only elevated pre-transplant but also post-transplant levels sCD30 levels must be measured [7], [19], [20], [21], [22]**.** Other researches did not find significant of pre/post-sCD30 with the graft function in KT because the very heterogeneous factors that affect this marker [23], [24], [25], [26].

We withdrew one sample sCD30 before, 13.4 ± 4.5 days pre-transplant and another sample after transplantation (19.5 ± 9.2) days post-transplantation for each patient, in addition to the control group. Our research found that there was a significant relation between pre/post-samples of sCD30 with showed increasing sCD30 levels after transplantation.

In time; our study showed no significant association between sCD30 and AR or any of BPAR episodes, PRAR, CAD.

Furthermore, many authors found heterogeneous results of the meta-analysis from 12 studies and concluded that the accuracy of sCD30 for predicting graft rejection was poor and their explanation for this observed heterogeneity due to many factors such as heredity, host susceptibility, and environmental factors [27], [28]. In addition, Halim *et al*. made several measurements of this marker post-transplantation but they recorded that serial measurements of sCD30 did not show a difference among subjects who displayed AR episodes [29]. Moreover, Slavcev *et al*. recommended measurement of soluble CD30 after transplantation, taken into consideration with the presence of HLA class II antibodies, might be helpful for evaluating the potential risk for AR [30].

Contrary to our results, there was a strong association between sCD30 and the risk of AR detected by other investigators [2], [4].

Accordingly, we can summarize and explain some facts about these results. Serum levels of sCD30 are increased in our transplant patients independently of graft rejection or functions. Although other researchers found that increased sCD30 levels could be affected by many factors, it is not only limited to T-cells activity but also on B-cell lines [8]; however, in this research, we assess only one aspect of the immune system. Pellegrini *et al*. confirmed our opinion that showed *in vitro*, under physiological conditions; CD30 is not a marker for Th2 cells only but an important co-stimulator molecule in the regulation of the Th1/Th2 balance [31]**.** This may explain the lack of a sustained association

between sCD30 release and graft functions and the different biomarkers after allogeneic transplantation. Moreover; as we said before, we could not assess HLA class II antibodies which may be affected on sCD30.

There is another factor in the height of this marker; during allogeneic stimulation of T cells, CD30 is upregulated on the memory CD4+and CD8+T cells and the CD30 will thus release into the blood, but at the same time, the receptors decrease with the time [32] and become more resistant; upon these facts, we put a hypothetical theory that its increase in serum but with no activity on the receptors. Finally, we realized that donor type was an important factor leading to the heterogeneous results in the studies.

Some studies added that the gender and the age of the patients considered from the heterogeneous factors that could affect the sCD30 results; but our results not supported this fact; subgroup analyses showed neither significant correlation between levels of sCD30 with the gender factor nor with the age of patients [33], [34]. In agreement with us, Azarpira *et al*. showed no relation between the effect of sCD30 and the age of patients with rejection [25].

Another important factor that controls the effect of sCD30 is the type of the graft. All our patients were from living donors. Whether related or non-related, Mirzakhani *et al*. talked about another important point that controls the effect of this marker on which is the type of the transplant whether cadaveric or living donor. They found a strong association relation between sCD30 levels and AR, but this effect was moderate in the patients who received the graft from living donors [2].

Our results concluded that there is no effect of IS drugs on post-transplant sCD30 level. As the same of our results, some of the studies reported that the sCD30 level was not significantly different after IS drugs [7], [35], [36], [37]. Others reported that IS drugs may affect the sCD30 level and decrease the post-transplant sCD30 levels [2].

Risk assessment in KT is complex and dependent on multiple factors of immunologic factors. Accordingly, we recommend the future studies that it needs large-scale multicenters studies; and taking into consideration, serial measurements for every patient; and according to those factors, patients can be stratified into higher and lower risk categories before the introduction of sCD30 as biomarker into the clinical practice.

Limitation

This study was limited by being a single-center study and the lack of serial measurement of the sCD30 marker to verify its pattern of expression after KT.

Conclusions

We found a significant increase in serum sCD30 levels after KT than before transplantation which suggests its over expression in KTRs probably due to activated immune response. Serum levels of sCD30 did not show any significant difference AR nor in CAD groups. Further, larger scale study is recommended with serial assessment of this marker which could be useful in detecting its role in allograft function and pathology.

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