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Increased level of advanced glycation end-products in renal transplant patients is associated with decreased measured GFR and grafted kidney function

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ABSTRACT

Background: Advanced glycation end-products (AGEs) cause proinflammatory responses and macromolecular damages. Advanced oxidation protein products (AOPPs) are protein biomarkers for oxidative stress. Levels of AGEs and AOPPs increase with the progression of chronic renal dysfunction.

Objectives: In this study, we aimed to measure these species in patients with renal transplantation and to analyze their correlation with the measured glomerular filtration rate (GFR) and renal function parameters.

Patients and Methods: Eighty renal transplant patients and normal subjects were recruited. GFR was measured by the two-sample plasma method with technetium-99m-labeled diethylenetriaminepentaacetic acid (TC^{99m}-DTPA) clearance. Biochemical measurements included creatinine, cystatin C, urea, total protein, and pentosidine. Serum AGEs were determined using a fluorometric assay and AOPPs were estimated spectrophotometrically.

Results: The measured GFR found to be significantly decreased in renal transplant patients compared to the control subjects ($P<0.001$). Levels of AGEs, AOPPs, serum creatinine, and cystatin C were increased in renal transplant patients with lower values of measured GFR (mGFR). A significant association between the levels of AGEs species (serum fluorescence and pentosidine) and mGFR when adjusted for creatinine and other risk factors in multiple linear regression model analysis was found ($P=0.05$ and $P=0.001$, respectively).

Conclusions: This study demonstrated increased levels of pentosidine and AGEs in transplant recipients were associated with decreased mGFR. Their accumulation can be predictive for the progression of chronic allograft loss of function.

Implication for health policy/practice/research/medical education:
Advanced glycation end-products (AGEs) are harmful species which are involved in many pathological conditions such as complications of diabetes and chronic allograft nephropathy. Studying the involvement and damages of these compounds in renal transplant patients can shed more light to the molecular mechanisms of this situation and may be implicated in the early detection and treatment of chronic deteriorations of the transplanted kidney.

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Original Article

1. Background

Advanced glycation end-products (AGEs) are products of non-enzymatic reactions between ketones or aldehydes and the amino groups of proteins, lipids and nucleic acids that are known as the Maillard reaction (1). In the presence of hyperglycemia and/or oxidative stress conditions, the reaction results in the formation of reversible Schiff base adducts which further rearrange to more stable covalently-bound Amadori products (1, 2). AGEs are composed of multiple molecular species including pentosidine, N^{ε}-(Carboxymethyl)lysine and pyralline (3). Among the AGE species, pentosidine is commonly measured as a marker of AGEs formation. In chronic kidney disease (CKD) increased levels of pentosidine can be seen as a result of decreased excretion and enhanced formation in response to oxidative/carbonyl stress condition. Reactive carbonyl species are formed during reactive oxygen species attack to carbohydrates and lipids (4). It has been shown that uremia, in non-diabetic patients with kidney disease, is associated with accumulation of AGEs. This indicates the significant influence of renal function on AGE levels (3).

Renal transplantation is the most effective therapy to reduce elevated levels of AGEs in blood and tissues and is the ultimate therapy in end-stage renal disease patients (5). Despite significant achievements in preventing acute allograft rejection, the chronic progressive dysfunction of the transplanted kidney has not been successfully managed (6). The most important cause of renal allograft impairment after first year is poorly defined. Up to 40% of transplanted kidneys develop chronic dysfunction after few months posttransplant which result in failure within a decade (7).

Advanced oxidation protein products (AOPPs) are protein indicators of oxidative stress in patients with uremia. Their plasma levels increase with the progression of chronic renal dysfunction (8). AOPPs along with AGE-proteins which have similar structures induce proinflammatory responses and macromolecular damages. Impaired renal function and dialysis are associated with high levels of these species (9).

Previous evidence supports the role of AGEs in the progression of graft dysfunction (4). In non-transplant individuals, aging, diabetes and renal dysfunction augment AGEs levels. In kidney transplant patients, enhanced AGE formation occurs which can be attributed to immunosuppressive therapy, donor conditions, mismatch of human leucocyte antigen (HLA), and progressive loss of function of the graft (10). It is suggested that AGE accumulation is responsible for the deterioration of the transplanted kidney.

2. Objectives

The aim of the present study was to evaluate serum AGEs, pentosidine and AOPPs levels in renal transplant patients and to analyze their correlation with the measured GFR using TC^{99m}-DTPA clearance and other renal function parameters. In addition, their levels were compared in different transplant patients categorized based on CKD stages to study their association with chronic allograft dysfunction.

3. Patients and Methods

3.1. Patients

The study population consisted of 80 renal transplant patients and normal subjects, which were recruited from the Golestan hospital in Ahvaz, Iran. The study was conducted at the Ahvaz Jundishapur University of Medical Sciences (AJUMS). Patients with different durations post renal transplantation with stable conditions were introduced by an expert nephrologist. Blood samples were obtained from all postrenal transplant patients and serum was separated immediately by centrifugation and stored at -70°C for future analysis.

3.2. GFR measurement

Glomerular filtration rate (GFR) was measured by the two-sample plasma method with Technetium-99m-labeled diethylenetriaminepentaacetic acid (TC^{99m}-DTPA) clearance which is a reliable method for measuring GFR. In two sample GFR measurement, gamma scan of kidneys was performed to obtain renogram following the radiolabel injection along with drawing timed samples after 60 and 180 minutes. The radioactivity of the samples and standard preparations were quantified using a gamma scintillation counter. Before scanning, patients were hydrated enough and their height and weight were recorded to determine the body surface area (BSA). Kidney size and GFR value are proportional to body size, Thus GFR was normalized to BSA using the DuBois method {BSA (m2) = [71.84 weight (kg) 0.425 × height (cm)0.725] / 10 000} (11). The measured GFR using this method is denoted as measured GFR (mGFR) throughout the paper. Renal transplant patients were categorized based on CKD stage K/DOQI classification using mGFR.

3.3 Biochemical measurements

Levels of creatinine, urea, total protein and albumin in serum were measured using standard diagnostic kits from Pars-Azmun (Iran). Serum creatinine was measured by the Jaffe method, serum urea by an enzymatic method based on urease glutamate dehydrogenase, serum total protein by the Biuret method and serum albumin by a colorimetric method with Bromocresol Green using a

biochemistry autoanalyzer (Biotecnica BT 3000 Plus, Italy).
Serum levels of cystatin C were quantified using a commercial ELISA kit (Biovendor, Brno, Czech Republic). The assay included a sandwich enzyme immunoassay using a specific capture antibody and an HRP-labeled antibody. Procedures were performed according to the manufacturer's protocol.

3.4. Measurement of advanced glycation end-products

A simple, fluorometric assay was used to estimate total serum AGE levels in kidney transplant patients. Serum AGEs were determined fluorometrically upon excitation at 350 nm and emission detection at 440 nm using a fluorescence spectrometer (Thermo Scientific Lumina, South Korea). Briefly, serum was diluted 1:50 with PBS (pH=7.4) and fluorescence intensity were measured and expressed in arbitrary units (AU) normalized to total protein content (AU/g protein) (9,12).
Pentosidine concentration in serum was determined using a commercial ELISA kit (Cusabio Biotech, Wuhan, China). Quantification procedure was performed according to the manufacture's protocol. In brief, 50 µL of serum samples were incubated with pentosidine antibody-coated wells. Following washing, the HRP conjugated antibody was added. After 1 hour incubation, the excess conjugated antibody was washed out and the extent of TMB substrate conversion was measured spectrophotometric by a plate reader at 450 nm. Results were expressed as pmol/mL.

3.5. Measurement of advanced oxidation protein products

AOPPs were estimated spectrophotometrically in serum at 340 nm using Chloramine-T standard, as described previously (12,13). In brief, 200 µL of PBS-diluted serum (1:5, pH = 7.4), as well as 200 µL of serial concentrations of chloramines-T (0-100 µmol/L) for calibration and 200 µL of PBS as blank were placed into a microplate. KI (10 µL, 1.16 M) and acetic acid (20 µL) were loaded into the wells and their absorbance was measured immediately at 340 nm using a spectrophotometer (UV/VIS spectrophotometer, Jasco 7850). Concentrations of AOPPs are expressed as chloramine units (µmol/g protein).

3.6. Ethical issues

The study protocol was in accordance with the Helsinki Declaration and it was approved by the ethics committee of Ahvaz Jundishapur University(ajums.REC.1393.123). Informed consent was obtained from all participants to be included in the study.

3.7. Statistical analysis

Quantitative data are expressed as mean ± SD (n = 80). Following testing for normality, independent *t* test was used to compare the parameters in transplant recipients and healthy subjects. Linear univariable and multivariable regression analysis were performed to determine the relationship between the parameters and the measured GFR. Levels of the measured parameters in different patients, categorized based on mGFR were compared using analysis of variance (ANOVA) test. Values of $P < 0.05$ were considered statistically significant.

4. Results

We investigated 80 adults (34 females and 46 males) with renal transplantation. The subjects' age ranged from 19 to 65 years. Clinical characteristics, serum levels of AGEs and AOPPs and renal function parameters are shown in Table 1. The mean values of AGEs, AOPPs, serum creatinine, and cystatin C were increased in renal transplant patients compared to the normal subjects. The mGFR found to be significantly decreased in renal transplant patients compared to the estimated GFR in the control group ($P < 0.001$).
In order to investigate the association of AGEs and AOPPs with the renal function in transplant recipient patients, regression analysis was performed. As shown in Table 2, there was a significant association between the levels of AGEs species (serum fluorescent AGEs and pentosidine) and AOPPs with the measured GFR ($P < 0.001$, and $P = 0.04$, respectively). Using multiple

Table 1. Demographic and biochemical characteristics of the subjects

	Normal subjects (n = 40)	Transplant recipients (n = 80)	*P* value
Age (y)	38.5 ± 5.1	42.7 ± 12.9	-
Gender (F/M)	12/28	34/46	-
AOPP (µmol/g protein)	2.7 ± 0.9	10.39 ± 7.83	<0.001
AGE (AU/g protein)	4.21 ± 0.83 × 10^3	9.39 ± 3.81 × 10^3	<0.01
Serum pentosidine (pmol/mL)	175.18 ± 92.95	3596.47 ± 588.3	<0.001
Serum creatinine (mg/dL)	0.92 ± 0.3	2.05 ± 1.31	<0.01
Serum cystatin C (mg/L)	0.79 ± 0.15	1.89 ± 0.57	<0.001
mGFR (mL/min/1.73 m^2)	104.4 ± 19.2*	52.94 ± 17.12	<0.001

* GFR was estimated in normal subjects using CKD-EPI creatinine-cystatin equation.

Table 2. Univariate regression analysis of factors related to mGFR in renal transplant patients

Variable	β	*P* value
Gender (F/M)	-0.23	0.05
Age (y)	0.02	0.88
BMI (kg/m²)	-0.01	0.93
Time post transplant (y)	-0.02	0.06
Creatinine (mg/dL)	-0.70	0.00
Cystatin C (mg/L)	-0.72	0.00
AGEs (AU/g protein)	-0.53	0.00
Pentosidine (pmol/mL)	-0.48	0.00
AOPPs (μmol/g protein)	-0.26	0.04

BMI, body mass index; AGEs, serum fluorescent advanced glycation end-products; AOPPs, serum advanced oxidation protein products; β, represents standardized regression coefficient.

linear regression model analysis, the association between serum fluorescent AGEs and pentosidine and mGFR remains significant when adjusted for a number of risk factors including age, sex, body mass index (BMI), time post-transplantation, and creatinine (β = -0.21, $P=0.05$; β = -0.35, $P=0.001$ respectively). But the association of AOPPs with mGFR did not remain significant in this model (β = 0.12, $P=0.27$). In addition, serum creatinine and cystatin C levels were highly correlated with the Tc^{99m}-DTPA clearance and the mGFR (r = -0.701 and r = -0.744 respectively, $P<0.001$).

Kidney recipient patients were categorized according to their mGFR based on CKD stages classification. Values of serum AGEs, AOPPs and pentosidine were determined in the patients of each category. As shown in Figure 1, comparison of the levels of serum fluorescent AGEs and pentosidine in patients with different CKD stages showed that there was an inverse relationship between kidney function and AGEs levels and higher levels of AGEs were found in progressed stages of CKD ($P<0.01$). Similarly, levels of AOPPs were found to be significantly increased in patients with the GFR below 30 mL/min which were denoted as stage 4 patients ($P<0.05$). Additionally, the mean serum AGEs, pentosidine and AOPPs in all patients with different mGFR levels were higher than the values of these parameters in healthy subjects (Table 1).

5. Discussion

This study was performed to investigate the association of AGEs and oxidative markers with the decline in renal function in kidney transplant patients. These patients have experienced excessive AGEs accumulation before transplantation during renal function loss and dialysis. Kidney transplantation restores renal function and lowers AGEs levels but they remain higher than normal (14,15). Progressive deterioration of kidney function starts early after transplantation and eventually leads to graft losses.

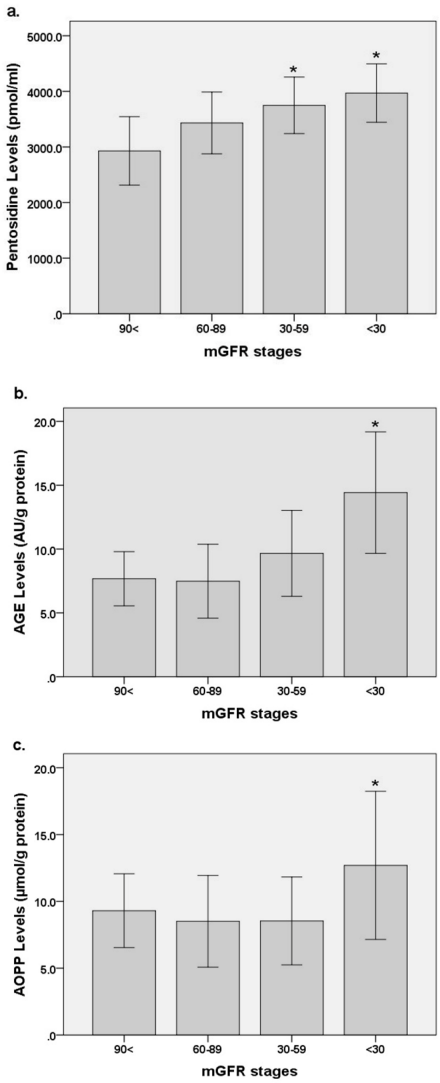

Figure 1. Levels of serum pentosidine (a), fluorescent AGEs (b), and AOPPs (c) in renal transplant patients with different mGFR values. The classification was adopted from the common CKD stages. *$P<0.01$ for AGEs and $P<0.05$ for AOPPs vs. stages I and II (with mGFR 60-89 mL/min per 1.73 m² or higher).

Knowledge of the underlying mechanisms is necessary to manage this function loss (6). It has been proposed that AGEs contribute to the progression of graft dysfunction (14), and graft loss (16). It has been reported that serum AGE levels might be associated with the decrease in renal function in renal transplant patients, and suggested them as a biomarker for evaluating the grafted kidney function (17).

Our results showed a significant association between AGEs levels and the grafted kidney GFR measured by Tc^{99m}–DTPA clearance even after adjustment for creatinine level. Higher AGEs levels were found in advanced stages of function loss. These finding further suggest the involvement of AGEs in this process. In addition to removing AGEs, the kidney is also a site

for AGEs accumulation (18). AGE-related damages are mediated directly through accumulating and linking to tissue components and by interaction with the receptors for AGEs (RAGEs). This interaction causes reactive oxygen species formation, inflammation and fibrosis mediated by NF-κB and MAP kinase signaling pathways (6).

Risk factors for the development of chronic dysfunction of a transplanted kidney including the length of dialysis before transplantation, the age of the donor, and primary graft function are parameters for AGEs accumulation. Decreased excretion of AGEs and enhanced oxidative stress during impaired kidney function result in the accumulation of AGEs. In addition to damaging the transplanted kidney, oxidative stress and inflammation are intricately linked to AGE formation (10). It is well demonstrated that stable renal transplant recipients have a pattern of increased oxidative stress. Chronic renal failure, inflammation, diabetes mellitus, reperfusion injury and immunosuppressive medications are among determinants of oxidative stress.

Our results showed that the renal transplant patients have significantly higher advanced oxidation protein products compared to healthy subjects and levels of these oxidation products were found to be significantly increased in patients with the mGFR below 30 mL/min which are the patients with advanced stage of transplant kidney dysfunction. These results are similar to the findings of Antolini et al, who showed increased levels of oxidative stress-related factors such as albumin-bound pentosidine, AGEs, AOPPs and low-molecular-weight carbonyls (LMW-C) in kidney transplanted patients with uremia and chronic allograft nephropathy. Oxidative stress and AGEs accumulation due to increased precursor catalysts of the Maillard reaction and decreased renal detoxification of reactive carbonyl species in uremia were identified as important factors in the progression of the graft dysfunction (19). It is suggested that the increased AGEs levels in these patients cannot be attributed solely to the decreased renal function (14).

In this study, using a multiple linear regression model analysis we observed a significant negative association between the mGFR and levels of AGEs following controlling for creatinine accumulation and other risk factors. This elevation in AGEs levels might not only be due to renal insufficiency but also can be causative to the progressive deterioration of the transplanted kidney.

Serum creatinine levels provide inaccurate estimates of GFR in renal transplant patients. The use of more accurate parameters such as TC^{99m}–DTPA measured GFR and cystatin C for determining renal function could shed further light on the relationship between impaired renal function and pentosidine or AOPPs accumulation. In addition, the effects of corticosteroid therapy on stimulating the metabolic pathways leading to the pentosidine formation and their catabolic effect on enhancing the generation of nonglucose precursors of AGEs should be considered (20).

Slowik-Zylka et al, reported that there were significant correlations between free pentosidine and parameters of transplanted kidney function including serum creatinine, urea, and estimated GFR in the late measurements post transplantation, but they failed to show the correlations for total pentosidine (4). This finding indicates the important role of time in the development of biochemical and graft changes that should be noted in interpreting the results.

In our study, the results did not show a significantly adjusted association between AOPPs and the measured GFR in renal transplant recipients. Similarly, Zadražil et al suggested that long-term administration of immunosuppressive agents is involved in the increased formation of AOPPs following transplantation and did not find significant associations between AOPPs or total antioxidant substance (TAS) and estimated GFR (21). The oxidative stress monitoring by AOPPs and modulation of total oxidative status by antioxidant treatment seems to be necessary to improve renal transplant patients health (22). Inhibition of AGE formation has also been considered as a useful adjunct therapy to prevent chronic allograft damaging (23).

In our study, the duration of partially restored kidney function after transplantation was associated with AGEs accumulation but did not reach the significant level ($P = 0.06$). A detective cycle of progressive deterioration mediated by increasing tissue AGEs, oxidative stress and immunosuppressive therapies can be proposed.

The extent of AGEs formation may provide a useful marker for monitoring the transplanted kidney and can improve the ability to detect early signs of the graft deterioration. In addition, AGEs are not merely markers of renal failure and may provide opportunities for intervention by using AGEs inhibitors to improve renal function. Prospective trials using anti-AGEs therapies can further confirm the role of AGEs in the progression of chronic renal transplant dysfunction.

6. Conclusions

This study demonstrated increased levels of pentosidine, AGEs and AOPPs in renal transplant recipients that were associated with decreased mGFR. It is suggested that levels of AGEs and pentosidine can be predictive for the development of chronic allograft dysfunction. AGEs can be considered as potential targets for pharmacologic intervention to inhibit the chronic deteriorations of transplanted kidney. Further studies are warranted to

evaluate this application.

Limitations of the study

In this study we measured a limited number of AGE species and we suggest to investigate more AGE compounds in studies with larger sample size. In addition, we could not measure the GFR with the reference method in healthy subjects due to the ethical considerations.

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Authors' contribution

All the authors have contributed towards performing the study and preparation of the manuscript and they all have approved the latest version of the article.

Conflicts of interest

The authors declare no conflict of interests.

Ethical considerations

Ethical issues (including plagiarism, misconduct, data fabrication, falsification, double publication or submission, redundancy) have been completely observed by the authors.

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