Journal of Diabetes and Its Complications 31 (2017) 1384–1388

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

No evidence for progressive deterioration in stimulated insulin secretion in renal transplant recipients after 12 years tacrolimus exposure

Mariëlle A.C.J. Gelens [a,*], Johannes P. van Hooff [a], Len Usvyat [b,c], Maarten H. Christiaans [a]

[a] Department of Internal Medicine, Maastricht University Medical Centre, PO-box 5800, 6202 AZ Maastricht, The Netherlands
[b] Renal Research Institute, 315E 62nd ST, New York, NY 10065, USA
[c] Fresenius Medical Care North America, 950 Winter St, Waltham, MA 02451, USA

ARTICLE INFO

Article history:
Received 13 April 2017
Received in revised form 29 June 2017
Accepted 3 July 2017
Available online 4 July 2017

Keywords:
Renal transplantation
Tacrolimus (Tac)
Insulin secretion
Insulin resistance
Post transplantation diabetes mellitus (PTDM)
NODAT

ABSTRACT

Aims: Tacrolimus (Tac) inhibits insulin secretion in a Tac-trough blood level dependent way *early* post-transplant in renal transplant recipients (Rtx). It is unknown whether *long-term* exposure results *into a progressive* beta cells dysfunction.
Methods: Two independent cohorts of Tac-treated non-diabetic Rtx, previously participating in glucose metabolism studies using intravenous Glucose Tolerance Test (ivGTT) were included: Fifty-eight Rtx were tested by ivGTT cross-sectional between 0.25 and 12.6 years post-transplant. Factors related to glucose metabolism parameters were explored by multilinear regression analysis. Eighteen non-diabetic Rtx tested by ivGTT 6 months post-transplant were retested at 12 years. The glucose metabolism outcome parameters were also adjusted according to the results of the cross-sectional study.
Results: Multivariate analysis showed *'Age'*, *'BMI'* and *'use of steroids'* to be significantly related, in different combinations, to the glucose metabolism parameters *'insulin resistance'*, *'fasting insulin level'* and *'stimulated insulin secretion'*. However *'time on tacrolimus'* wasn't related to any parameter.
In the longitudinal study, none of the glucose metabolism parameters (either analyzed crude or adjusted) deteriorated clinically or statistically significant. Numerically, *'stimulated insulin secretion'* even increased.
Conclusions: Chronic Tac exposure does NOT lead to a progressive decrease in *'stimulated insulin secretion'* between 6 months and 12 years post renal transplant in our population of 18 patients.

1. Introduction

Annually, 120,000 solid organ transplants are performed in the world, according the World Health Organization. Tacrolimus (Tac) is the most prescribed immunosuppressive maintenance therapy in solid organ recipients[1] and used by patients for many years.

Hyperglycemia occurs very frequent in the first months after solid organ transplantation.

The use of the immunosuppressive drug Tac and the use of glucocorticosteroids are established risk factors. Tac inhibits insulin secretion in a level dependent way, and steroids increase insulin resistance.[2,3,4]

In the first months after transplantation target levels of Tac are between 10 and 20 ng/ml and steroid dosages are high. Thereafter target levels of Tac are lower between 5 and 10 ng/ml and steroid dosages are tapered. Since it has been shown that lowering of Tac target levels will result in less inhibition of insulin secretion,[3] and steroids dosages have been decreased considerably it is understandable that hyperglycemia will disappear in many patients.

However hyperglycemia will persist in a proportion of patients, especially in those who had low capacity of insulin secretion before transplantation.

Persistent hyperglycemia has been called Post transplantation Diabetes Mellitus (PTDM).

Although also later after transplantation PTDM does occur, its incidence is much lower than in the early period.[5,6] However, it is unknown whether *long-term* exposure to Tac results into progressive decrease in insulin secretion. To explore this relationship, we performed a cross sectional study in a group of Tac-treated renal recipients without PTDM >3 months post-transplant to explore for donor, recipient and transplant factors (including *'time on tacrolimus'*) which might be related to parameters of basal and stimulated glucose metabolism.

Furthermore, long-term changes in basal and stimulated glucose metabolism was studied by ivGTT both at *6 months* and at *12 years* post-transplant in an independent cohort of Tac-treated renal transplant recipients without signs of PTDM at month 6 post-transplant.

Conflict of Interest Statement: The authors have no conflict of Interest.

* Corresponding author at: Maastricht University Medical Center, PO-box 5800, 6202 AZ Maastricht, The Netherlands.
E-mail addresses: m.gelens@mumc.nl (M.ACJ. Gelens), hooffvan@xs4all.nl (J.P. van Hooff), Len.Usvyat@fmc-na.com (L. Usvyat), m.christiaans@mumc.nl (M.H. Christiaans).

http://dx.doi.org/10.1016/j.jdiacomp.2017.07.001
1056-8727/

2. Subjects, materials and methods

These studies were approved by the Medical Ethical Committee (MEC) of the Maastricht University Medical Centre (MEC numbers 104,084 and 114,006).

2.1. Patients

2.1.1. Part I

A cross-sectional cohort of all 58 Caucasian, renal transplant recipients with Tac-based immunosuppressive regimen from time of transplant onwards, in which an ivGTT was performed in the past as part of previous studies on glucose metabolism.[2,7] Everyone was normo-glycemic according the American Diabetes Association (ADA)-criteria[8] pre- or post-transplant. None of these patients participated also in the longitudinal study Part II.

2.1.2. Part II

The study cohort included adult renal recipients without diabetes per the American Diabetes Association (ADA) criteria, who received a Tac-based immunosuppressive regimen from transplantation to the end of the study periods, and had available intravenous glucose tolerance test (ivGTT) results from participation in previous studies on glucose metabolism early after transplantation.[3,4] The patients included in the study had previous ivGTT tests performed at 6 months after renal transplantation. For investigation of (potential) chronic Tac-induced beta cell toxicity, ivGTT testing was performed during a long term follow up period. All patients were Caucasians, which is reflective of our primary population in North West Europe.

A total of 18 patients were identified for the study and had data collected from clinical and hospital medical records. Of these, four patients could not be invited to be retested with ivGTT: two died, one had a graft loss, and one patient was converted to another immunosuppression because of suspicion of Tac-related neurotoxicity. Fourteen patients with a functional graft that remained on a Tac-based immunosuppressive regimen were contacted for informed consent to perform a second ivGTT; 13 patients provided consent for the investigation.

For the five patients who could not be retested by ivGTT at the second time point, the clinical and laboratory details are given in the section results.

2.2. Basal and stimulated glucose metabolism by ivGTT

In both studies, glucose (fasting and ivGTT samples) was measured in whole blood by the UV-Hexokinase method (LX, Beckman Coulter, Mijdrecht, the Netherlands). For insulin, the Autodelfia method (Wallac, Turku, Finland) was used.

The ivGTT tests were performed in the morning, after a 12-hour overnight fast. Tac was ingested after completion of the tests. Glucose 50% (0.5 g/kg body weight, maximum 75 g glucose) was administered intravenously for 2 to 3 min. Venous blood samples for measuring glucose and insulin were taken from the opposite arm at the following time (t) points: $t = -15$, 0, 5, 10, 15, 20, and 30 min (min).

The insulin sensitivity index (glucose disappearance rate) was calculated by linear regression from the log-transformed glucose values of $t = 10$ to 30 min. A glucose disappearance rate value below 0.8% per min was considered abnormal, between 0.8 and 1.2% per min as intermediate, and above 1.2% per min as normal.

Stimulated insulin secretion was calculated as Area Under the Curve using a linear trapezoidal technique from the serum value at each time point from $t = 0$ to 30 min after subtraction of the $t = 0$ value.

Insulin resistance was calculated using the homeostasis model assessment (HOMA-R: fasting glucose (mmol/L) multiplied by fasting insulin (mU/L) divided by 22.5).[9]

2.3. Statistics

Statistical analysis was performed using the SPSS package, version 20 (IBM, the Netherlands).

2.3.1. Part I

A multilinear regression analysis, using both stepwise forward selection and backward elimination techniques, was performed with the following glucose metabolism parameters as outcome parameters: *'fasting insulin'*, *'homeostasis model assessment for insulin resistance (HOMA-R)'*, *'stimulated insulin secretion'*, *'fasting glucose'*, and *'glucose disappearance rate'*. In this analysis the following variables were used as suspected risk factors: *'age'*, *'body mass index (BMI)'*, *'estimated glomerular filtration rate (eGFR)'*, *'time on tacrolimus'*, *'Tac trough level'*, and *'use of glucocorticoids (yes vs. no)'* (this is use of glucocorticoids at this time/time of ivGTT). There were no missing data. Outcome parameters are given as mean with standard deviation (sd). The search for the best fitting regression model containing only significant associations was done. The final model had to have a P-value < 0.05. For being included in the final model, individual parameters had to have a P-value < 0.05 in the forward selection technique, or P-value < 0.10 in the backward elimination technique.

2.3.2. Part II

To compare relevant clinical parameters and glucose metabolism at both time points after renal transplantation, a paired Wilcoxon signed rank test was used for continuous data. The McNemar test was used for dichotomous nominal data. A P-value < 0.05 (two-sided tested) was considered to be statistically significant. Unless indicated otherwise, data are presented as median values and ranges.

3. Results

3.1. Part I: cross sectional

3.1.1. Study population

The characteristics of the 58 patients are shown in Table 1. They are representative for our renal transplant population with inclusion of patients from early (3 months) to late (up to >12 years) after renal transplantation. Sixteen patients (28%) used steroids in their immunosuppressive regimen (seven patients 5 mg and nine patients 10 mg prednisone). The high number of patients being steroid-free represents our center immunosuppressive protocol.[10]

3.1.2. Glucose metabolism parameters

Mean fasting glucose was 5.6 mmol/L (sd. 0.86) and mean fasting insulin 7.6 mU/L (sd. 4.5). Mean HOMA-R was 2.15 mmol/L * mU/L (sd. 1.25). Mean stimulated insulin secretion was 818.2 mU * min/L (sd. 630.3), and mean glucose disappearance rate was 1.56 mmol/L per min (sd. 0.74).

Table 1
Relevant characteristics of Part I (cross-sectional study group; $n = 58$).

	Mean or percentage	SD	Median	Range
Mean age recipient during ivGTT (years)	52.6	12.6	56.3	20.9–75.5
Male sex (percentage)	72%			
Time on tacrolimus (years)	4.4	3.4	3.4	0.23–12.6
BMI (kg/m^2)	25.5	3.5	24.5	20.0–36.6
MDRD (ml/min/1.73m^2)	51,5	16.6	48.8	6.4–84.0
Tacrolimus trough-level (sd.)	7.1	2.4	6.6	4.0–17.3
Glucocorticoids (%)	28%			
Glucocorticoids use (5 mg) $n = 7$ (years)	2,7			
Glucocorticoids use (10 mg) $n = 9$ (years)	0,53			
Acute rejection (%)	14%			