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Original Article

Intensive monitoring for post-transplant diabetes mellitus and treatment with dipeptidyl peptidase-4 inhibitor therapy

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ABSTRACT

Aim: Current monitoring practices fail to diagnose patients with post-transplant hyperglycaemia and tend to delay initiation of treatment, which potentially results in adverse graft and morbidity outcomes. This real-world study set out to assess the impact on insulin resistance indices of a new clinical pathway for diagnosis and treatment of hyperglycaemia following renal transplantation.

Methods: A hundred and forty-seven adult renal transplant recipients, without pre-existing diabetes, from a single centre were included. Patients transplanted between January 2008 to September 2015 formed the historical cohort. Patients transplanted between October 2015 and February 2018 were subject to a new clinical pathway - if they had fasting blood sugar levels more than 7 mmol/L or random blood glucose levels more than 11.1 mmol/L, they had early introduction of oral therapy, using the DPP-4 inhibitor linagliptin.

Results: In the historical cohort, 19.8% were diagnosed with PTDM, compared to 46.3% in the protocol cohort. Amongst patients with PTDM, there was a significant difference in HOMA-IR ($p = 0.02$) between the historical cohort (median HOMA-IR 3.33) and the protocol cohort (median HOMA-IR 2.21). There was a significant difference at each time point (0,1,2-h measurements) of blood glucose levels form oral glucose tolerance testing between patients with and without PTDM in the historical cohort ($p < 0.001$), but no difference between patients in the protocol cohort.

Conclusion: Detection of PTDM was higher with the new clinical pathway. Early treatment of hyperglycaemia resulted in better insulin resistance scores. Larger prospective controlled studies focussing on early detection and management of PTDM with linagliptin are warranted.

1. Introduction

Post-transplant diabetes mellitus (PTDM) occurs in up to 50% of solid organ transplant recipients within the first year [1,2]. In addition to traditional risk factors for diabetes such as obesity and family history, the use of immunosuppressants including corticosteroids and calcineurin inhibitors (CNIs) increase insulin resistance and exhibit direct toxicity to beta cells [2,3]. PTDM is associated with an increased risk of all-cause cardiovascular mortality and risk of acute rejection [4,5]. Inadequate surveillance and reliance on morning rather than peak BGLs can result in underdetection of diabetic range BGLs and delayed treatment, as proved by the peak effect of steroids and greater post-prandial effects in the afternoon [6].

PTDM is traditionally managed with lifestyle modifications and optimization of immunosuppressants (where possible), followed by metformin or sulphonylureas, then escalation to insulin therapy [7]. Recent consensus guidelines suggest the use of insulin as first line treatment for early post-transplant hyperglycaemia [8]. However, patients may be reluctant to use injectable agents, and there

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are additional economic and time costs involved with the administration, education and monitoring for side effects [9]. The combination of insulin and steroids may result in a vicious cycle of weight gain and increasing insulin resistance [10,11]. As beta-cell failure is a prominent component of PTDM, early treatment may minimize beta-cell stress and protect against the development of PTDM [1,12–14]. Dipeptidyl-peptidase 4 (DPP-4) inhibitors potentiate incretin function, inhibit glucagon release and increase insulin secretion and are not associated with the same hypoglycaemia risks of sulfonylureas. In pre-clinical models, DPP-4 inhibitors have demonstrated efficacy in preserving beta cell function under stress [15]. Thus, the use of DPP-4 inhibitors could offset the CNI-induced toxic effect on beta cells and improve insulin resistance. Linagliptin is a DPP-4 inhibitor that does not have the side effects associated with insulin or metformin use, and does not require dose adjustment with reduced renal function as is commonly seen in the early post-transplant setting [16].

We commenced a programme of surveillance for elevated blood glucose levels (Fig. 1) in our transplant unit with early introduction of linagliptin for PTDM. We used BGLs, oral glucose tolerance test (OGTT) results and HOMA scores to compare the effect of linagliptin to conventional therapy using a historical cohort of patients from our unit managed under the same immunosuppressive protocols.

2. Research design and methods

The purpose of this retrospective cohort study was to assess whether intensive surveillance for elevated BGLs post-transplant and early introduction of oral anti-diabetic therapy was effective in the management of PTDM and reduced B cell toxicity. The project was approved by the Sir Charles Gairdner and Osborne Park Health Care Group (HREC 2015-057). This protocol introduced more intense monitoring than previously and emphasized afternoon measurements of BGLs, to improve detection of peak glucose levels, which occur between 2 and 4pm [6].

2.1. Study population

All patients who had received a renal transplant between October 2015 and February 2018 were included in the new clinical pathway during their hospital stay and in clinics post-discharge, and formed the “protocol cohort”. Patients were diagnosed with PTDM if they had more than two readings of a fasting blood glucose level (fBGL) of >7 mmol/L or random blood glucose levels of >11.1 mmol/L at least 48 h post-transplantation. These patients were commenced on linagliptin 5 mg as illustrated in Fig. 1. Patients who remained hyperglycaemic on linagliptin therapy had additional medications added as per the protocol in Fig. 1. OGTTs were performed 3 months -post-transplantation.

All patients who were transplanted between January 2008 and September 2015 (including patients from the study by Rosettenstein et al.) [17] formed the “historical cohort”. These patients had been given conventional treatment (e.g. metformin, insulin, sulphonylureas) if PTDM had been detected usually based on morning fBGLs as per the American Diabetes Association criteria, Each group was subdivided into patients who had PTDM diagnosed within a year of transplantation and those who did not. The immunosuppression regimen with Basiliximab™ & methylprednisolone induction and prednisolone, tacrolimus and Myfortic™ maintenance remained unchanged between 2008 and 2018. Target tacrolimus levels for all patients was set to 8–12 in the first month, then 5–10 thereafter. Patients who had not had an OGTT performed within 1 year of transplantation, did not have clinic letters or details on history of diabetes, development of PTDM or medications lists were excluded from this study (Fig. 2).

2.2. Data collection

Data were collected from paper and electronic health care records. Baseline patient characteristics included age, gender, body mass index (BMI, defined as weight (kg)/height (m) [2]), cause of end-stage renal disease; donor characteristics included type of donor (living, or deceased and whether they were an extended criteria donor) and transplant-related characteristics including transplant date and age at transplantation. For blood glucose records, fasting insulin and BGL, and 1-h and 2-h BGLs after a 75 g oral glucose load were extracted from OGTT results.

HOMA-IR scores were calculated with the formula [18,19]:

$$\text{HOMA}-\text{IR} = \frac{\textit{fasting glucose}\,(\textit{mmol/litre}) \times \textit{fasting insulin}\,(\textit{units})}{22.5}$$

HOMA-β percentages were calculated with the formula:

$$\text{HOMA}-\beta = \frac{(20 \times \textit{fasting insulin}\,(\textit{units}))}{(\textit{fasting glucose}\,(\textit{mmol/litre}) - 3.5)}\ \%$$

2.3. Statistical analysis

Subject data was divided into a historical cohort (before October 2015) and a protocol cohort (October 2015 onwards). Patients in each cohort were divided into those with PTDM and those without. For each patient, fasting insulin level, and BGL measurements at baseline (fasting), 1- and 2-h at approximately 3 months post-transplantation. Descriptive statistics were based on frequency distributions for categorical data and means and standard deviations or medians, inter-quartile-ranges, and ranges for continuous data, depending on normality. Univariate analysis between groups included χ [2] and Fisher Exact tests, as appropriate, for categorical comparisons, and one-way ANOVA or non-parametric Mann-Whitney U or Kruskall-Wallis tests for comparison of continuous outcomes. Non-parametric Spearman's Rho correlation coefficients were used to describe the correlations between fBGLs and HOMA B% at baseline. Linear mixed models incorporating random subject effects were used to examine differences in BGL measurements between and within groups over time. Results were summarised as predicted marginal means and corresponding 95% confidence intervals. Statistical analysis conducted and Fig. 3 created using Stata 15.0 (StataCorp LLC, College Station, Texas). All hypothesis tests were 2-sided, and a P values of <0.05 were considered statistically significant.

3. Results

Of the 482 patients who had received a renal transplant between 2008 and 2018, 147 met inclusion criteria for the review and had the required clinical and biochemical details available. 106 patients formed the historical cohort and 41 patients formed the protocol cohort. In the historical cohort, 21 patients (19.8%) were diagnosed with PTDM. In the protocol cohort, 19 patients (46.3%) were diagnosed with PTDM (Table 1).

The average age of patients was 51.5 years, with 87 males (59.2%). The average pre-transplant body mass index (BMI) was 27 kg/m^2. There was no significant difference between age, sex or BMI between the 4 groups ($p = 0.51$, $p = 0.32$ and $p = 0.14$ respectively). Ninety-seven patients (66%) received a kidney from a deceased donor. There was no significant difference in the donor type between the groups ($p = 0.22$).

For those diagnosed with PTDM, the median time to OGTT in the

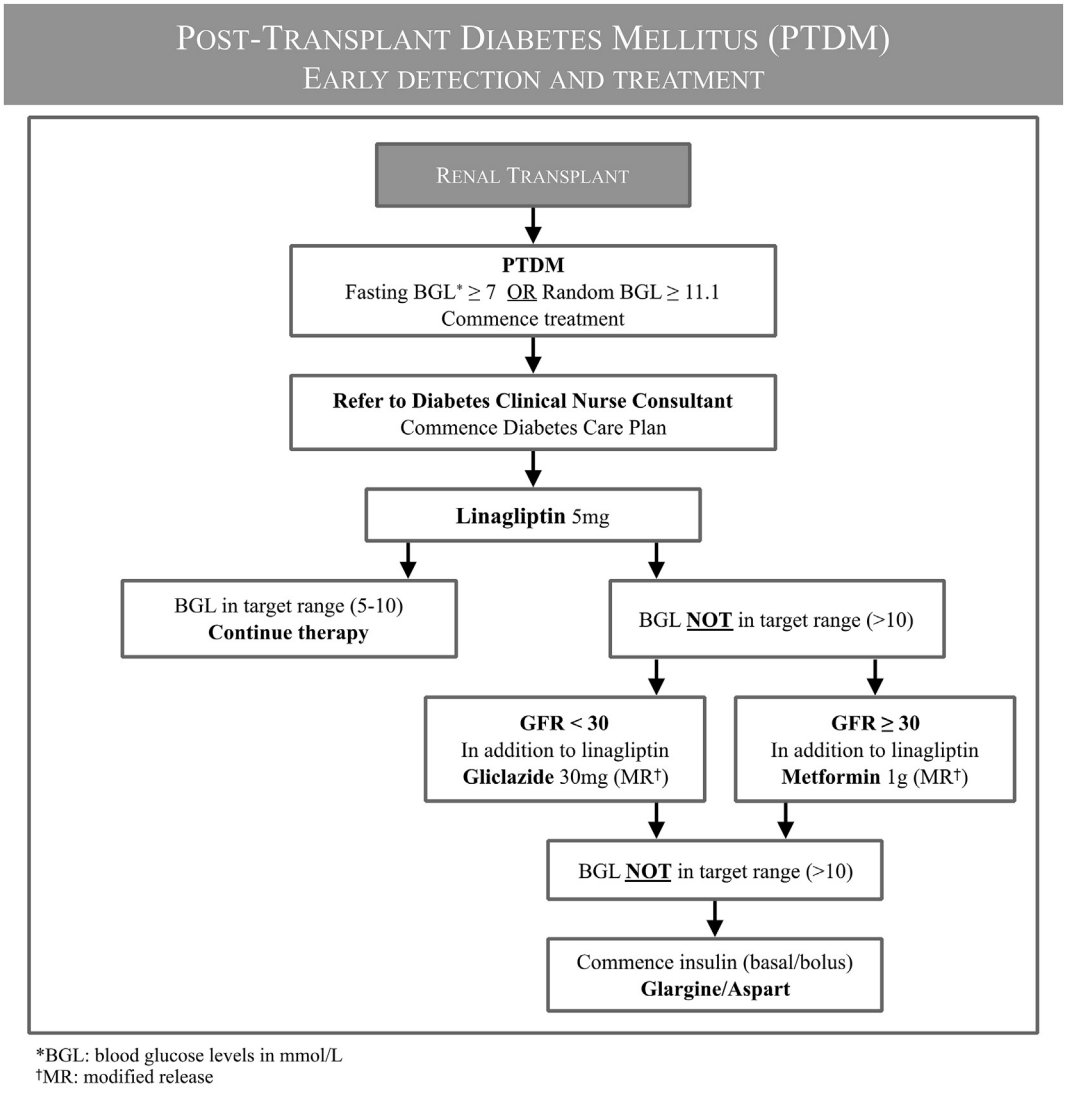

Fig. 1. Protocol for management of patients post renal transplant with high blood glucose measurements.

historical cohort was 93 days post-transplantation and in the protocol group, 95 days post-transplantation. There was no significant difference between the groups overall or within cohorts. Linagliptin was started a median of 90 days post-transplantation. Six of the 19 patients required an additional agent in the protocol group (Table 2).

The median HOMA-IR scores were 1.64 and 1.86 in the historical and protocol groups without PTDM respectively. Amongst patients with PTDM, the median HOMA-IR in the historical group was 3.33 vs 2.21 in the protocol group ($p = 0.02$). In the historical cohort, the median HOMA-β was 110% for patients without PTDM, and 81% for those with. In the protocol cohort, these were 101% and 100% respectively. There was no significant difference between the protocol and historical groups for patients who had PTDM ($p = 0.27$).

When the individual blood glucose results from OGTT samples were measured, there was a significant difference at each time point (0,1,2-h measurements) between patients with and without PTDM in the historical cohort ($p < 0.001$), but no difference

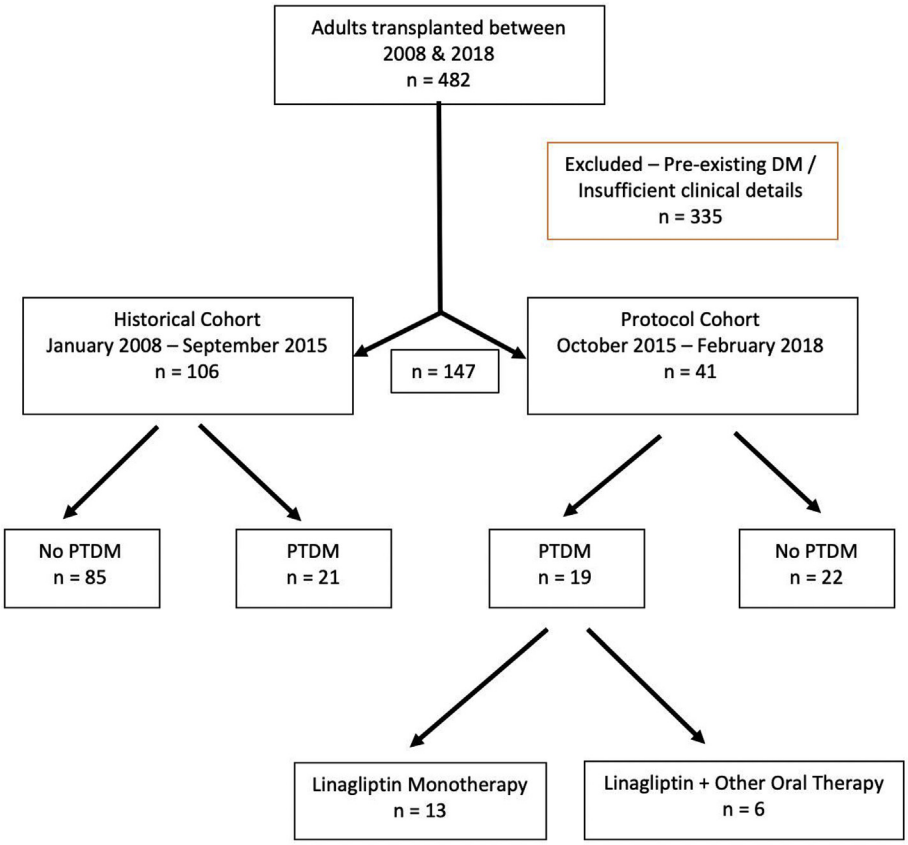

Fig. 2. Study population flowchart.

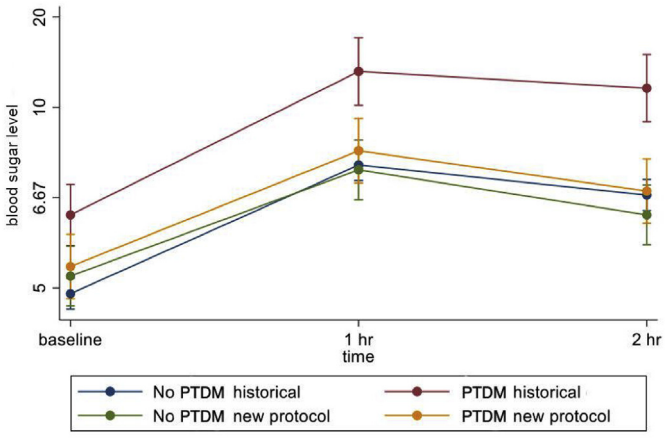

Fig. 3. Oral glucose tolerance test: blood sugar results at fasting, 1-h and 2-h time points for each cohort and sub-group of patients with fixed portion linear prediction applied. Higer values demonstrate worse control of blood sugar levels.

between patients in the protocol cohort ($p = 0.67$, 0.94 and 0.29 respectively, Table 1, Fig. 3).

4. Discussion

With the high rates of hyperglycaemia post-transplant (up to 50% of recipients diagnosed with PTDM). The diagnosis of PTDM in the post-transplant setting is controversial. The American Diabetes Association Guidelines defines it as hyperglycaemia after the initial 6 months post-transplantation [11]. Furthermore, the lack of longitudinal data in transplant recipients has resulted in different approaches to PTDM (non-pharmacological measures, insulin treatment, oral agents). One could question the need for treatment of hyperglycaemia in the early phase post-transplantation. However, from general population studies, we know that early treatment of at-risk patients with pharmacotherapy reduced further incidence of diabetes, improved insulin sensitivity and this in turn has a legacy effect, as seen in the UKPDS trial [20,21]. For these reasons, this study was undertaken to assess the benefits of increased surveillance and early treatment with an oral agent.

Traditional oral agents, such as metformin and gliclazide require dose adjustment for renal function (which varies in the initial post-transplant period) and have significant side effects including gastro-intestinal upset and hypoglycaemia. Vildagliptin, a DPP-4 inhibitor, has been shown to improve B-cell function in PTDM [22] and sitagliptin has been shown to improve HbA1c in kidney transplant recipients [23]. However, linagliptin is the only DPP-4 inhibitor that doesn't require dose adjustment in renal impairment but there is limited evidence of its efficacy in this population. A single retrospective study of linagliptin in India found it to be well tolerated and effective for glycaemic control in PTDM [24]. For these reasons, we chose to use linagliptin in the protocol cohort in our study.

A consensus statement in 2014 concluded that HbA1c would not be sensitive enough to rule out PTDM in the early post-transplant period, and that the OGTT has been long used in the general population and a predictor for long term outcomes [8]. As such we used OGTT in place of HbA1c in our study. Homeostatic model of assessment insulin resistance (HOMA-IR) and β-cell mass function (HOMA-β) scores are derived from OGTT results, have been used widely in the literature to determine insulin resistance, and

Table 1
Descriptive summary of patients included in the study of demographics, donor type, duration post-transplantation, HOMA IR and B results.

N = 147		Historical cohort*		Protocol cohort**		p	p*	p**	p#
		No PTDM *n = 85*	PTDM *n = 21*	No PTDM *n = 22*	PTDM *n = 19*				
		n (%)	*n (%)*	*n (%)*	*n (%)*				
Sex *missing n = 3*	M	53 (63.9)	11 (52.4)	10 (45.5)	13 (68.4)	0.318	0.236	0.122	0.239
	F	30 (36.1)	10 (47.6)	12 (54.5)	6 (31.6)				
Donor	Unknown	2 (2.4)	1 (4.8)	1 (4.5)	0 (0.0)	0.015	0.877	0.287	0.215
	AKX	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)				
	DBD	15 (17.6)	6 (28.6)	13 (59.1)	6 (31.6)				
	DCD	23 (27.1)	5 (22.7)	2 (9.1)	4 (21.1)				
	DCD L/K	2 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)				
	DD	16 (18.8)	3 (14.3)	0 (0.0)	0 (0.0)				
	ECD	0 (0.0)	0 (0.0)	0 (0.0)	2 (10.5)				
	LRD	17 (20.0)	5 (23.8)	3 (13.6)	3 (15.8)				
	LURD	9 (10.6)	1 (4.8)	3 (13.6)	4 (21.1)				
Age* *mean (sd) [min-max]* *missing n = 2*		49.7 (11.9) [22–73]	53.2 (9.9) [31–73]	52.9 (13.5) [18–74]	50.3 (12.4) [16–68]	0.505	0.206	0.520	0.406
Days post-transplant OGTT done* *med (IQR) [min-max]*		90 (90, 91) [64–178]	93 (90, 100) [71–161]	98 (89, 113) [81–322]	95 (83, 135) [76–254]	0.144	0.492	0.666	0.486
HOMA IR* *med (IQR) [min-max]* *missing n = 2*		1.64 (1.09, 2.16) [0.37–10.75]	3.33 (1.98, 4.12) [1.38–7.04]	1.86 (1.22, 2.38) [0.87–5.97]	2.21 (1.33, 2.88) [0.82–5.8]	<0.001	<0.001	0.395	0.019
HOMA B%* *med (IQR) [min-max]* *missing n = 2*		110 (83, 154) [21–386]	81 (44, 116) [18–857]	101 (69, 156) [23–250]	100 (67, 168) [21–580]	0.234	0.035	0.990	0.270
BGL* *mean (sd) [min-max]* *missing n = 2*		5.0 (0.9) [4.2–11]	6.8 (2.3) [4.2–12.6]	5.3 (0.8) [4.4–9.3]	5.5 (1.3) [4.4–9.3]	<0.001	0.002	0.442	0.031
BMI *missing n = 3*		26.2 (5.1)	27.8 (4.4)	24.6 (3.9)	27.3 (5.4)	0.139	0.183	0.068	0.765

N.B Data summarised as *n (%) unless specified otherwise**.
p*Historical cohort: No PTDM vs PTDM.
p** Protocol cohort: No PTDM vs PTDM.
p# PTDM old vs PTDM new.
p Comparison of 4 groups.

Table 2
Hypoglycaemic agents used (for protocol cohort, in addition to linagliptin therapy).

Hypoglycaemic agent	Historical cohort*		Protocol cohort**	
	No PTDM *n = 85*	PTDM *n = 21*	No PTDM *n = 22*	PTDM *n = 19*
Metformin only	–	5	–	–
Other or >1 agent		14		6
Insulin only	–	1	–	–

correlate well to burden of disease and mortality outcomes [18,19,25].

The increased surveillance for PTDM through the protocol resulted in a higher proportion (46.3% vs 19.8%) of the protocol cohort being identified to have PTDM. Within the patients in the historical cohort, there was the expected difference in HOMA-IR scores between those who had PTDM versus no PTDM (3.33 vs 1.64, $p < 0.001$). In the protocol cohort, however, there was no significant difference between the groups with and without PTDM (1.86 vs 2.21, $p = 0.40$). This, along with the fact that OGTTs were performed at a similar time in the subgroups, suggests that early diagnosis and treatment of PTDM has a protective effect against the development of insulin resistance. Furthermore, patients with PTDM in the protocol group had similar HOMA-IR scores to those without PTDM and better HOMA-IR scores than those who were treated with conventional therapy (2.21 vs 3.33, $p = 0.02$), consistent with the islet-cell protective role identified in pre-clinical studies. Although not statistically significant, conventional treatment (metformin/insulin) resulted in B-cell function lower than that of patients from the historical and protocol cohorts without PTDM and those who were treated with linagliptin (HOMA-B: 81% vs 110%, 101%, 100% respectively, $p = 0.23$). These results suggest that at an average of 100 days post-transplant, treatment with linagliptin resulted in B-cell function that was equivalent to patients who did not have diabetes, an effect not seen with conventional treatment. With each timepoint during the OGTT result, patients who were treated with linagliptin, had significantly better results than those in the conventional therapy arm, and these results were very similar to patients who did not develop PTDM in the first place (Table 1, Fig. 3).

Limitations of this study include its small sample size, retrospective, single centre set-up without a concurrent control group. The lower rates of PTDM observed in the historical cohort are likely to be due to the less intensive monitoring protocol. Some patients in the protocol group did not have OGTT done due to transfer to secondary follow-up units and thus were excluded from the study.

5. Conclusion

The prevalence of diabetes after transplantation has been steadily increasing and confers significant risk to affected individuals [10]. Although many patients with post-transplant hyperglycaemia will return to euglycaemia with reduction in immunosuppression, a substantial proportion of patients will have persistently impaired glycaemic control. We challenged the current guidance on treatment of PTDM on the basis of population data,

which emphasises the benefits of early intervention in reducing glucotoxicity and further stressing pancreatic function. Despite the fact that intensive monitoring within the three month period (as is in this study) could lead to overdiagnosis of hyperglycaemia post-transplant, we propose that this will lead to legacy benefits in our at-risk population [26].

With similar baseline characteristics and post-transplant immunosuppression, we compared intensive surveillance and early commencement of oral therapy to conventional treatment in a historical cohort of patients. Patients who were treated with linagliptin had better HOMA-IR and HOMA-B scores, and had better BGL at every timepoint after a glucose load. BGL and HOMA measurements in those who were treated with linagliptin were very similar to those who did not develop PTDM.

Our real-world study suggests that intensive monitoring of BGLs and oral monotherapy with DPP4 inhibitor linagliptin is a promising treatment for the majority of kidney transplant recipients who develop PTDM and may help reduce insulin resistance. Given the favourable side-effect profile and tolerability of these agents, larger prospective controlled studies focussing on early detection and management of PTDM are warranted.

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None.

Author contributions

Dr Aron Chakera – Supervisor, design & implementation of clinical protocol and manuscript author.

Dr Srivathsan Thiruvengadam – Design, data extraction, analysis, manuscript author and guarantor.

Mrs Angela Jacques – statistical analysis and interpretation of data.

Mr. Brett Cawley – data extraction and tabulation from database.

Mr. Shreyas Thiruvengadam – Data manipulation and manuscript edits.

Dr Kirsten Bennett – Clinical data extraction and manuscript edits in the pilot study.

Dr Brian Hutchison – Provision of historical cohort data.

Dr Wai Lim – Provision of historical cohort data, design and manuscript review.

Gloria Daniels – Clinical implementation of new protocol.

Narelle Cusack – Clinical implementation of new protocol.

All authors have made significant contributions to the conception and design of the work, and worked on data acquisition and analysis. The drafts and final versions have been critically revised by all, and we remain accountable for all aspects of work including the integrity of any part of the manuscript.

Conflicts of interest

The authors declare that they have no conflict of interest.

Compliance with ethical standards

This study has been approved by the Human Research Ethics Committee (Department of Health, Western Australia), and has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

All persons gave their informed consent prior to the inclusion in this study. The study database was anonymized and the initial non-anonymized data remained on encrypted hospital medical record servers.

Data sharing statement

Individual de-identified participant data will be listed on the University of Western Australia data repository. The data is available from time of publication and stored on an encrypted drive. Any other medical researcher who wishes to have access to our data can do so through email over the next 5 years.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2019.04.020.

References

[1] Hecking M, Haidinger M, Döller D, et al. Early basal insulin therapy decreases new-onset diabetes after renal transplantation. J Am Soc Nephrol 2012;23(4):739–49. https://doi.org/10.1681/ASN.2011080835.

[2] Montori VM, Basu A, Erwin PJ, Velosa JA, Gabriel SE, Kudva YC. Post-transplantation diabetes: a systematic review of the literature. Diabetes Care 2002;25(3):583–92.

[3] Group TA to CCR in DS. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358(24):2545–59. https://doi.org/10.1056/NEJMoa0802743.

[4] Luan FL, Samaniego M. Transplantation in diabetic kidney failure patients: modalities, outcomes, and clinical Management. Semin Dial 2010;23(2):198–205. https://doi.org/10.1111/j.1525-139X.2010.00708.x.

[5] Ganji MR, Charkhchian M, Hakemi M, et al. Association of hyperglycemia on allograft function in the early period after renal transplantation. Transplant Proc 2007;39(4):852–4. https://doi.org/10.1016/j.transproceed.2007.03.030.

[6] Yates CJ, Fourlanos S, Colman PG, Cohney SJ. Divided dosing reduces prednisolone-induced hyperglycaemia and glycaemic variability: a randomized trial after kidney transplantation. Nephrol Dial Transplant 2014;29(3):698–705. https://doi.org/10.1093/ndt/gft377.

[7] Davidson J, Wilkinson A, Dantal J, et al. New-onset diabetes after transplantation: 2003 International consensus guidelines. Transplantation. In: Proceedings of an international expert panel meeting. Barcelona, Spain, 19 February 2003, vol. 75; 2003. SS3–24. https://doi.org/10.1097/01.TP.0000069952.49242.3E (10 Suppl).

[8] Sharif A, Hecking M, de Vries APJ, et al. Proceedings from an international consensus meeting on posttransplantation diabetes mellitus: recommendations and future directions. Am J Transplant 2014;14(9):1992–2000. https://doi.org/10.1111/ajt.12850.

[9] Edelman S, Pettus J. Challenges associated with insulin therapy in type 2 diabetes mellitus. Am J Med 2014;127(10 Suppl):S11–6. https://doi.org/10.1016/j.amjmed.2014.07.003.

[10] Hwang JL, Weiss RE. Steroid-induced diabetes: a clinical and molecular approach to understanding and treatment. Diabetes Metab Res Rev 2014;30(2):96–102. https://doi.org/10.1002/dmrr.2486.

[11] Shivaswamy V, Boerner B, Larsen J. Post-transplant diabetes mellitus: causes, treatment, and impact on outcomes. Endocr Rev 2016;37(1):37–61. https://doi.org/10.1210/er.2015-1084.

[12] Lane JT, Odegaard DE, Haire CE, Collier DS, Wrenshall LE, Stevens RB. Sitagliptin therapy in kidney transplant recipients with new-onset diabetes after transplantation. Transplantation 2011;92(10):e56–7. https://doi.org/10.1097/TP.0b013e3182347ea4.

[13] Sharif A, Baboolal K. Risk factors for new-onset diabetes after kidney transplantation. Nat Rev Nephrol 2010;6(7):415–23. https://doi.org/10.1038/nrneph.2010.66.

[14] Strøm Halden TA, Åsberg A, Vik K, Hartmann A, Jenssen T. Short-term efficacy and safety of sitagliptin treatment in long-term stable renal recipients with new-onset diabetes after transplantation. Nephrol Dial Transplant 2014;29(4):926–33. https://doi.org/10.1093/ndt/gft536.

[15] Shah P, Ardestani A, Dharmadhikari G, et al. The DPP-4 inhibitor linagliptin restores beta-cell function and survival in human isolated islets through GLP-1 stabilization. J Clin Endocrinol Metab 2013;98(7):E1163–72. https://doi.org/10.1210/jc.2013-1029.

[16] Jin L, Lim SW, Doh KC, et al. Dipeptidyl peptidase IV inhibitor MK-0626 attenuates pancreatic islet injury in tacrolimus-induced diabetic rats. PLoS One 2014;9(6):e100798. https://doi.org/10.1371/journal.pone.0100798.

[17] Rosettenstein K, Viecelli A, Yong K, et al. Diagnostic accuracies of glycated hemoglobin, fructosamine, and homeostasis model assessment of insulin

resistance in predicting impaired fasting glucose, impaired glucose tolerance, or new onset diabetes after transplantation. Transplantation 2015;100(7):1. https://doi.org/10.1097/TP.0000000000000949.

[18] Salgado ALF de A, Carvalho L de, Oliveira AC, Santos VN dos, Vieira JG, Parise ER. Insulin resistance index (HOMA-IR) in the differentiation of patients with non-alcoholic fatty liver disease and healthy individuals. Arq Gastroenterol 2010;47(2):165–9.

[19] Bonora E, Formentini G, Calcaterra F, et al. HOMA-estimated insulin resistance is an independent predictor of cardiovascular disease in type 2 diabetic subjects. Diabetes Care 2002;25(7):1135–41. https://doi.org/10.2337/diacare.25.7.1135.

[20] King P, Peacock I, Donnelly R. The UK Prospective Diabetes Study (UKPDS): clinical and therapeutic implications for type 2 diabetes. 1999. p. 643–8.

[21] Armato JP, DeFronzo RA, Abdul-Ghani M, Ruby RJ. Successful treatment of prediabetes in clinical practice using physiological assessment (STOP DIABETES). Lancet Diabetes Endocrinol 2018;8587(18):1–9. https://doi.org/10.1016/S2213-8587(18)30234-1.

[22] Werzowa J, Hecking M, Haidinger M, et al. Vildagliptin and pioglitazone in patients with impaired glucose tolerance after kidney transplantation: a randomized, placebo-controlled clinical trial. Transplantation 2013;95(3):456–62. https://doi.org/10.1097/TP.0b013e318276a20e.

[23] Vilsboll T, Rosenstock J, Yki-Jarvinen H, et al. Efficacy and safety of sitagliptin when added to insulin therapy in patients with type 2 diabetes. Diabetes Obes Metab 2010;12(2):167–77. https://doi.org/10.1111/j.1463-1326.2009.01173.x.

[24] Sanyal D, Gupta S, Das P. A retrospective study evaluating efficacy and safety of linagliptin in treatment of NODAT (in renal transplant recipients) in a real world setting. Indian J Endocrinol Metab 2013;17(Suppl1):S203–5. https://doi.org/10.4103/2230-8210.119572.

[25] Matthews DR, Hosker JP, Rudenski a S, Naylor B a, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28(7):412–9. https://doi.org/10.1007/BF00280883.

[26] Conte C, Secchi A. Post-transplantation diabetes in kidney transplant recipients: an update on management and prevention. Acta Diabetol 2018;55(8):763–79. https://doi.org/10.1007/s00592-018-1137-8.