GLYCAEMIC DISTURBANCES AFTER PANCREAS TRANSPLANTATION

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INTRODUCTION

Though diabetes mellitus after transplantation (PTDM) has been studied extensively, there exists a patient group who develop dysglycaemia without need for insulin after pancreas transplantation. Rates are not well known, and estimates vary widely: 2-53% of patients developing hyperglycaemia and 30-50% developing hypoglycaemia (1-3). Rates of both abnormalities have rarely been studied in the same population, and the relationship to graft failure is not generally reported.

OBJECTIVES

- Complete a service evaluation of the rates of hypoglycaemia and hyperglycaemia after pancreas transplantation.
- Define distinguishing features associated with each group.
- Define relationship to graft failure.

METHODS

The study population is all pancreas transplant recipients with available GTT data from 2013 until April 2019. Sample population included patients with an abnormal GTT result and/or with self-reported symptoms of hypoglycaemia.

An abnormal GTT result is considered as either an impaired glucose tolerance (IGT) or one reaching diabetic levels. IGT is defined as a fasting value of 6.0-7.0 mmol/L and/or a post-prandial value of 7.9-11.0 mmol/L at 2 hours. Diabetic levels are a fasting value of over 7.0 mmol/L and/or over 11.0 mmol/L post-prandially (4). Mean BMI results were calculated for each patient, and a further mean for each group was taken to calculate 'mean BMI.' Latest BMI is the patient's most recent BMI result, on or before April 2019. The 'time to develop' had been calculated from the transplant date to the date of the first abnormal GTT result.

Using the Clinical and Welsh Portal databases, information was collected on: previous GTT, HbA1c, and C-peptide level results; weights and height; diagnosis and transplant dates; transplant failure. This was analysed and graphed using MATLAB software.

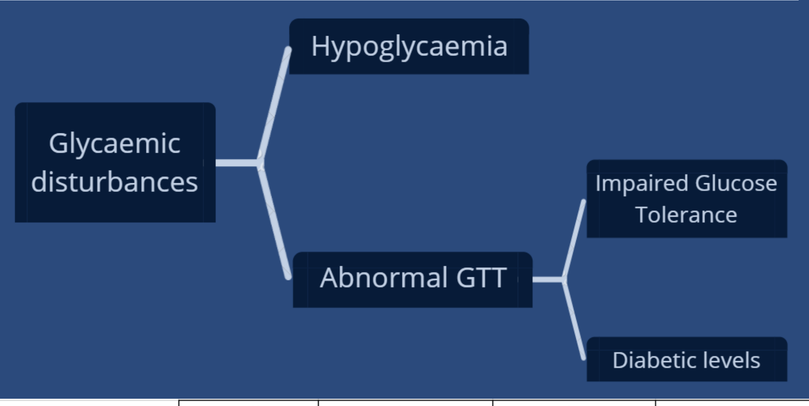
RESULTS

The sample population consisted of a total of 29 patients: 19 with an abnormal GTT result, 8 experiencing hypoglycaemia, and 2 with both, selected from 96 patients with GTT data. This included SPK (62%), PAK (21%) and PAT (17%) recipients aged 27-67, and currently represents 30% (29/96) of all pancreas transplant patients with GTT data. The abnormal GTT group consisted of 11 patients with GTT results of 'impaired glucose tolerance (IGT)' and 10 with those at 'diabetic' levels.

	C-peptide levels		mean BMI		BMI change		latest BMI		pre-transplant HbA1C		post-transplant HbA1C		Time to develop (months)	
	Hypo	Abnormal GTT	Hypo	Abnormal GTT	Hypo	Abnormal GTT	Hypo	Abnormal GTT	Hypo	Abnormal GTT	Hypo	Abnormal GTT	Hypo	Abnormal GTT
Mean	804	1144	23.7	27.6	-1.5	2.3	23.5	29.4	89.4	65.5	34.1	42.0	46	55
SD	245	610	3.7	4.0	5.5	5.6	4.0	6.1	20.5	18.9	5.5	4.6	29	39
***P* value**	0.043		0.017		0.090		0.010		0.011		0.00035		0. 579	
95% CI	629 - 980	850 - 1438	21.1 - 26.4	25.7 - 29.5	-5.4 - 2.4	-0.4 - 5.0	20.6 - 26.4	26.5 - 32.4	72.2 - 106.5	55.0 - 76.0	30.2 - 38.0	39.8 - 44.2	22 - 71	36 - 74

This project found hyperglycaemia to be twice as common as hypoglycaemia after transplantation (abnormal GTT group represents 22% (21/96), hypoglycaemia group 10% (10/96) of all transplants). Mean BMI revealed a significant difference between the two groups, with abnormal GTT patients having higher BMIs. Although the BMI change between pre- and post-transplant BMI did not reach statistical significance, there is a trend towards weight gain for hyperglycaemic patients and weight loss for hypoglycaemic patients. C-peptide levels were significantly higher in the abnormal GTT group than the hypo group. As expected, most recent post-transplant HbA1C levels between the two groups were significantly different. There was an unexpected difference found in pre-transplant HbA1C levels, with hypoglycaemic recipients having higher HbA1C results.

The mean time to develop an abnormality (until detected on GTT) was approximately 4 years, and there was no significant difference between the hypo- and hyperglycaemia groups. No patients in this dataset have reported the cessation or easing of hypoglycaemic symptoms, though 5 abnormal GTT patients (24%) have now achieved a normal GTT result spontaneously or through weight loss. Failure data revealed a failure rate of 10% for the hypoglycaemic group (1/10) and 5% for the abnormal GTT (1/21), compared to 12% for normoglycaemia (8/67).



	All dysglycaemia	Hyperglycaemia (IGT)	Hyperglycaemia (diabetic)	Hypoglycaemia
Mean time to develop (months)	52	61	51	46
Full range (months)	1 - 111	1 - 102	3 - 111	1 - 85
Number	29	11	10	10
Total population	96			
Rate	30%	11%	10%	10%

Figure 1. Table of rates of overall dysglycaemia and its subcategories, and of time to develop abnormality.

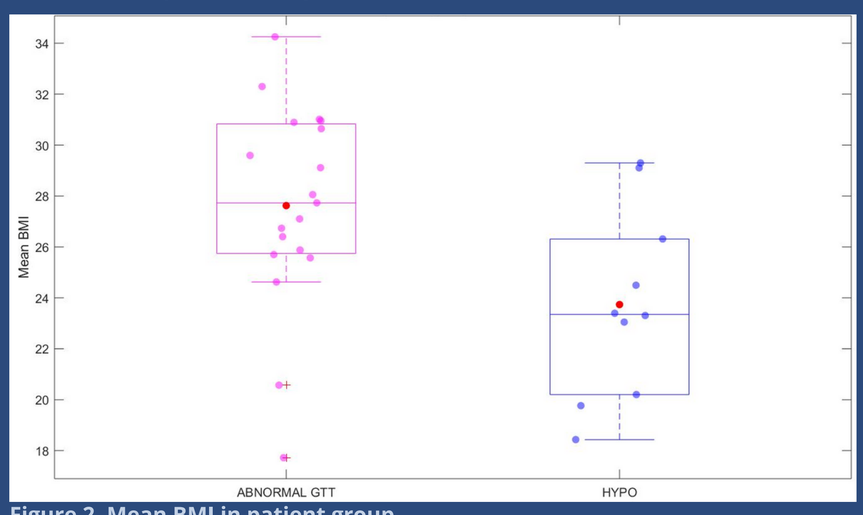


Figure 2. Mean BMI in patient group

DISCUSSION

Our project found hyperglycaemia (22%) to be twice as common as hypoglycaemia (10%). Previous data illustrating these rates is scarce; reports suggest 30-50% of transplantation patients experience hypoglycaemia (2,3,5). The rates of hyperglycaemia are more difficult to ascertain, and estimates vary between 2% and 53% (1).

No previous reports have directly compared hyperglycaemia and hypoglycaemia post-transplantation. Though many present a mean BMI for their dataset, only one found an association between weight gain and hyperglycaemia (6). This project has found abnormal GTT to be associated with higher BMI, higher C-peptide, and a trend towards weight gain post-transplant, with the opposite being true for hypoglycaemia. 24% of this dataset's abnormal GTT patients have now achieved a normal GTT, yet determining whether this improvement is due to spontaneous resolution, weight loss, or other factors is more subjective. Previous reviews have not directly compared C-peptide levels between hyper- and hypoglycaemic patients, but one paper found no difference in C-peptide between hypoglycaemic recipients and normoglycaemic recipients (7). An interesting finding is higher pre-transplant HbA1c levels in the hypoglycaemic group compared to the abnormal GTT group.

This evaluation is the first to consider 'time to develop' to distinguish this patient group from those associated with graft failure or diabetes recurrence. The failure rates for hypoglycaemic and hyperglycaemic recipients is similar to those of normoglycaemic recipients. This project, therefore, has not found an association of glycaemic disturbances with graft failure. Previous studies describe postoperative IGT as an early predictor of graft failure (8,9) however only data up to 14 days post-transplant was analysed, whereas our patient group developed abnormalities over a longer period of time.

CONCLUSION

Our most notable findings were:

- a comparison of rates of hyperglycaemia and hypoglycaemia;
- time to develop an abnormality is longer-term and similar in both groups; and
- no association with graft failure.

This evaluation reveals a need for better GTT implementation in clinics, and potential value in introducing continuous glucose monitoring. A main limitation has been a lack of standardisation in defining and managing post-transplant patients with hyper- or hypoglycaemia. Interesting differences found include higher HbA1c results in hypoglycaemic recipients, changes in weight, C-peptide, and mean BMI differences. These differences may have value as predictive features when compared to normoglycaemic recipients.

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REFERENCES

1. Davidson LJ, Wilkinson JA, Dantal CJ, Dotta CF, Haller CH, Hernandez CD, et al. NEW-ONSET DIABETES AFTER TRANSPLANTATION: 2003 INTERNATIONAL CONSENSUS GUIDELINES1. Transplantation. 2003;75(10 Suppl):SS3-SS24.
2. Zehrer CL, Gross CR: Prevalence of “low blood glucose” symptoms and quality of life in pancreas transplant recipients. C l i n Transpl 7:312–319, 1993
3. Larsen JL, Stratta RJ, Miller SA, Taylor RJ: Hypoglycemic symptoms following pancreas transplantation. Clin Tr a n s p l7:520–524, 1993
4. Organisation WH. Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia. Geneva, Switzerland: WHO; 2006.
5. Mittal, S., Franklin, R.H., Policola, C., Sharples, E., Friend, P.J. and Gough, S.C.L. (2015), Early postoperative continuous glucose monitoring in pancreas transplant recipients. Transpl Int, 28: 604-609. doi:10.1111/tri.12541
6. Neidlinger, N, Singh, N, Odorico, J, Sollinger, H, Pirsch, J. PREDICTORS OF NEW ONSET DIABETES AFTER PANCREAS TRANSPLANT: 83. Transplantation. 2008;86(2S):29. doi:10.1097/01.tp.0000332766.80711.f5.
7.Hypoglycemia after pancreas transplantation. J B Redmon, A U Teuscher, R P Robertson Diabetes Care Nov 1998, 21 (11) 1944-1950; DOI: 10.2337/diacare.21.11.1944
8. Mittal, S., Nagendran, M., Franklin, R.H. et al. Postoperative impaired glucose tolerance is an early predictor of pancreas graft failure. Diabetologia 57, 2076–2080 (2014). https://doi-org.abc.cardiff.ac.uk/10.1007/s00125-014-3320-y
9. Shapey, IM, Tan, ZL, Gioco, R, et al. Peri-transplant glycaemic control as a predictor of pancreas transplant survival. Diabetes Obes Metab. 2020; 1– 9. https://doi.org/10.1111/dom.14181