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DIABETIC Medicine

RESEARCH: COMPLICATIONS

Hyperglycaemia following immune checkpoint inhibitor therapy—Incidence, aetiology and assessment

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Abstract

Aims: We systematically studied the presence of hyperglycaemia during treatment with Immune Checkpoint Inhibitors (ICPI) for cancer, in those with and without diabetes at baseline, and determined the cause of new-onset hyperglycaemia,

Methods: Retrospective review of electronic records of those receiving an ICPI for melanoma, lung or renal cancer.

Results: Overall, 959 participants were included. In this study, 103 had diabetes at baseline (10.7%). Those with lung cancer had the highest frequency of diabetes; 131 people had hyperglycaemia (defined as at least one glucose ≥11.1 mmol/L) in the year after starting an ICPI. The incidence was 55% in those with diabetes at baseline, and 8.6% in those without baseline diabetes. Among 74 with new-onset hyperglycaemia (without pre-existing diabetes) 76% was attributable to steroid induced diabetes, with 9.5% due to ICPI Induced diabetes resembling type 1 diabetes.

Conclusions: Hyperglycaemia is common in persons receiving an ICPI for cancer, including 8.6% of those without known diabetes. While much of this is due to glucocorticoid use, care is needed to avoid missing those with ICPI-induced diabetes who are at risk of diabetic ketoacidosis, which is a medical emergency.

KEYWORDS
cancer, clinical diabetes

1 | INTRODUCTION

Over the last decade, Immune Checkpoint Inhibitors (ICPI) have resulted in a paradigm shift in cancer therapy.[1] From initially revolutionising the management of melanoma, ICPI are now used across multiple solid tumour types. ICPI works in a novel fashion, compared to existing cancer treatments, taking the brakes off a person's own immune system to enable it to target and attack the cancer,[2] by inhibiting the inbuilt checkpoint proteins, which normally control and contain our immune systems. A range of drugs have been developed to do this, including ipilimumab and tremelimumab (anti-CTLA-4), nivolumab and pembrolizumab (anti-PD-1) and avelumab, durvalumab and atezolizumab (anti-PD-L1). These drugs can cause a wide variety of immunotherapy specific toxicities, known as immune related adverse events, irAEs, caused by inflammation when the immune

system targets normal organs.[3] These adverse events can target any organ and some of the most common are endocrine irAEs.[4–6]

There has been much focus in recent years on ICPI induced diabetes, a condition that closely resembles type 1 diabetes, and is thought related to immune-mediated destruction of the beta cells.[7–13] Although clinically highly significant, usually leading to a life-long insulin requirement, and frequently presenting as diabetic ketoacidosis, this form of diabetes only affects 1%–2% of those receiving ICPI.

ICPI therapy itself can be associated with new onset hyperglycaemia by further mechanisms. Around a third of people treated with an ICPI require glucocorticoids for management of immune-related adverse events, often requiring high cumulative doses,[14] with between 6%–9% treated for melanoma developing steroid induced hyperglycaemia (SIH), based on retrospective review of routine tests.[14,15] This is likely to be higher in other cancers such as lung where people are typically older,[16] and as SIH is most marked later in the day,[17] clinic tests are likely to underestimate the true prevalence.

In addition to new onset hyperglycaemia following steroids, one study reported evidence of modest deterioration in glucose control among participants with type 2 diabetes following ICPI therapy,[18] perhaps due to increased inflammation, although no such effect was found in those without diabetes at baseline.

There have been few attempts to document the overall prevalence of hyperglycaemia during ICPI therapy, or to determine the actual frequency of different causes of hyperglycaemia. A meta-analysis of multiple studies reported hyperglycaemia related adverse events in 2.26% of people with 0.28% having severe adverse events, with higher rates in those receiving combination ICPI therapy (Ipilimumab and Nivolumab).[19] A second meta-analysis reported no increased risk of new-onset diabetes with ICPI therapy, but a hazard ratio for new-onset hyperglycaemia of 1.45, which only reached statistical significance in the placebo controlled studies.[20] Notably both these studies relied on reporting of diabetes or hyperglycaemia as adverse events in clinical studies, so are likely to be an underestimate of the real-world incidence of abnormal glucose levels following treatment.

Only one study has comprehensively examined glucose levels following ICPI treatment, reporting a markedly greater 27% incidence of hyperglycaemia post treatment, of which 28% was new-onset.[21] However, despite including over 400 people, no cases of immunotherapy induced autoimmune diabetes were detected, which limits any ability to compare the different causes of hyperglycaemia.

We have therefore examined the prevalence of diabetes at the time of starting ICPI therapy, and the incidence of hyperglycaemia in the year following treatment based on laboratory glucose levels in a single centre large cohort of people treated with an ICPI for melanoma, lung or renal cancer.

What's new?

- Hyperglycaemia can occur through multiple mechanisms in people with cancer treated with immune checkpoint inhibitors (ICPI).
- This study confirms a significant rate of hyperglycaemia in those with and without diabetes at baseline.
- The majority of hyperglycaemia is due to glucocorticoid use, but ICPI Induced diabetes occurs and may be hard to distinguish.
- We propose a management algorithm to safely diagnose and manage those with new onset hyperglycaemia after ICPI therapy for cancer.

2 | METHODS

People with lung, melanoma or renal cancer treated with an Immune Checkpoint Inhibitor at Royal Marsden Hospital between September 2010 and June 2021 were identified from pharmacy records. The hospital's electronic patient record system was used to determine the date of the person's first cycle of ICPI. The closest random glucose value to the start of treatment, as long as within 3 months, and any glucose levels ≥11.1 mmol/L in the year after treatment were extracted along with any HbA_{1c} results. Prescriptions of steroids from the cancer unit pharmacy were recorded. Age and BMI were extracted from the record at the time of starting ICPI.

Co-morbidities are not routinely coded on the electronic record unless a person is admitted. We therefore used a composite measure to determine diabetes status. All coded diagnoses for diabetes from admissions were collected, and we undertook free text searches of the electronic records, including all clinic letters, for words or phrases related to diabetes or its treatment. These extracts were then reviewed by a diabetes specialist, with review of the full electronic record where required to determine diabetes status.

Diabetes at baseline was recorded where:

1. There was a coded diagnosis of diabetes from an admission to the specialist cancer centre before starting ICPI OR

2. There was a coded diagnosis of type 1 or 2 diabetes from an admission to the specialist cancer centre after starting ICPI, following clinical review to ensure diagnosis pre-dated ICPI therapy (excluding those with Diabetes Not Otherwise Specified recorded after starting ICPI). OR
3. There was a recorded HbA_{1c} via the hospital laboratory ≥48 mmol/mol, 6.5% before the start of ICPI OR
4. The glucose closest to the start of ICPI was ≥11.1 mmol/L OR
5. A validated diagnosis of diabetes was confirmed after clinical review of the free text searches.

Hyperglycaemia on treatment was defined as a laboratory random venous glucose ≥11.1 mmol/L in the 12 months after starting ICPI. Hyperglycaemia was defined as new onset if there was no pre-existing diagnosis of diabetes according to the above case definition. This was classified as steroid induced hyperglycaemia if they were receiving glucocorticoids at a dose of >5 mg prednisolone or equivalent at the time of onset or in the previous 30 days. ICPI induced diabetes was defined as new onset hyperglycaemia in those not on glucocorticoids, but requiring insulin within 48 h of onset, and still requiring insulin at last follow up. Those not meeting either definition were regarded as unexplained hyperglycaemia.

Data were prepared in Excel and R with the use of Jamovi for data analysis. Continuous data were summarised with the median. Chi-squared tests were used to compare categorical variables and ANOVA or non-parametric equivalents for continuous variables.

The study was approved as a Service Evaluation by our Institution (Ref No SE1033) and as a retrospective review of medical records, participants' consent was not required.

3 | RESULTS

We identified a total of 959 participants; 703 had melanoma, 228 lung cancer and 28 renal cancer. Those with lung cancer were older and had a lower BMI (Table 1, Figure 1).

Overall, we identified 103 persons with diabetes at baseline, and 856 without; 131 persons had no glucose result available prior to starting ICPI, and 73 no glucose reading after ICPI. These people were excluded from analysis regarding glucose levels. As expected, those with diabetes were older, with a higher BMI, and a higher baseline glucose level (Table 2, Figure 1). People with Lung cancer were significantly more likely to have diabetes than those with renal cancer or melanoma (Table 1).

We then went on to examine the frequency of hyperglycaemia after starting treatment with an Immune Checkpoint Inhibitor. Overall, 131 persons had at least one glucose level >11.1 mmol/L within a year of starting treatment. Among those with lung cancer, 34 had hyperglycaemia and 153 did not, giving a hyperglycaemia rate of 15%. In those with melanoma 88 had hyperglycaemia and 615 did not, giving a rate of 12%, ($p = 0.272$ for comparison).

TABLE 1 Demographics by cancer type.

	Lung ($N = 228$)	Melanoma ($N = 703$)	Renal ($N = 28$)	Total ($N = 959$)	p value
AGE					<0.001[a]
Mean (SD)	66.1 (11.2)	59.7 (16.0)	59.1 (11.6)	61.2 (15.1)	
Range	27.0–91.0	12.0–92.0	38.0–81.0	12.0–92.0	
BMI					<0.001[a]
Missing	0	21	2	23	
Mean (SD)	25.0 (4.8)	26.6 (4.9)	28.3 (5.7)	26.3 (4.9)	
Range	14.9–44.3	16.2–48.8	18.7–43.3	14.9–48.8	
Glucose at start of treatment					0.003[a]
Missing	41	89	1	131	
Mean (SD)	6.9 (2.5)	6.3 (2.1)	6.6 (4.1)	6.4 (2.3)	
Range	3.8–20.9	2.8–23.8	3.6–25.4	2.8–25.4	
Diabetes at baseline					<0.001[b]
No	182.0 (79.8%)	649.0 (92.3%)	25.0 (89.3%)	856.0 (89.3%)	
Yes	46.0 (20.2%)	54.0 (7.7%)	3.0 (10.7%)	103.0 (10.7%)	

[a]Linear Model ANOVA.

[b]Pearson's Chi-squared test.

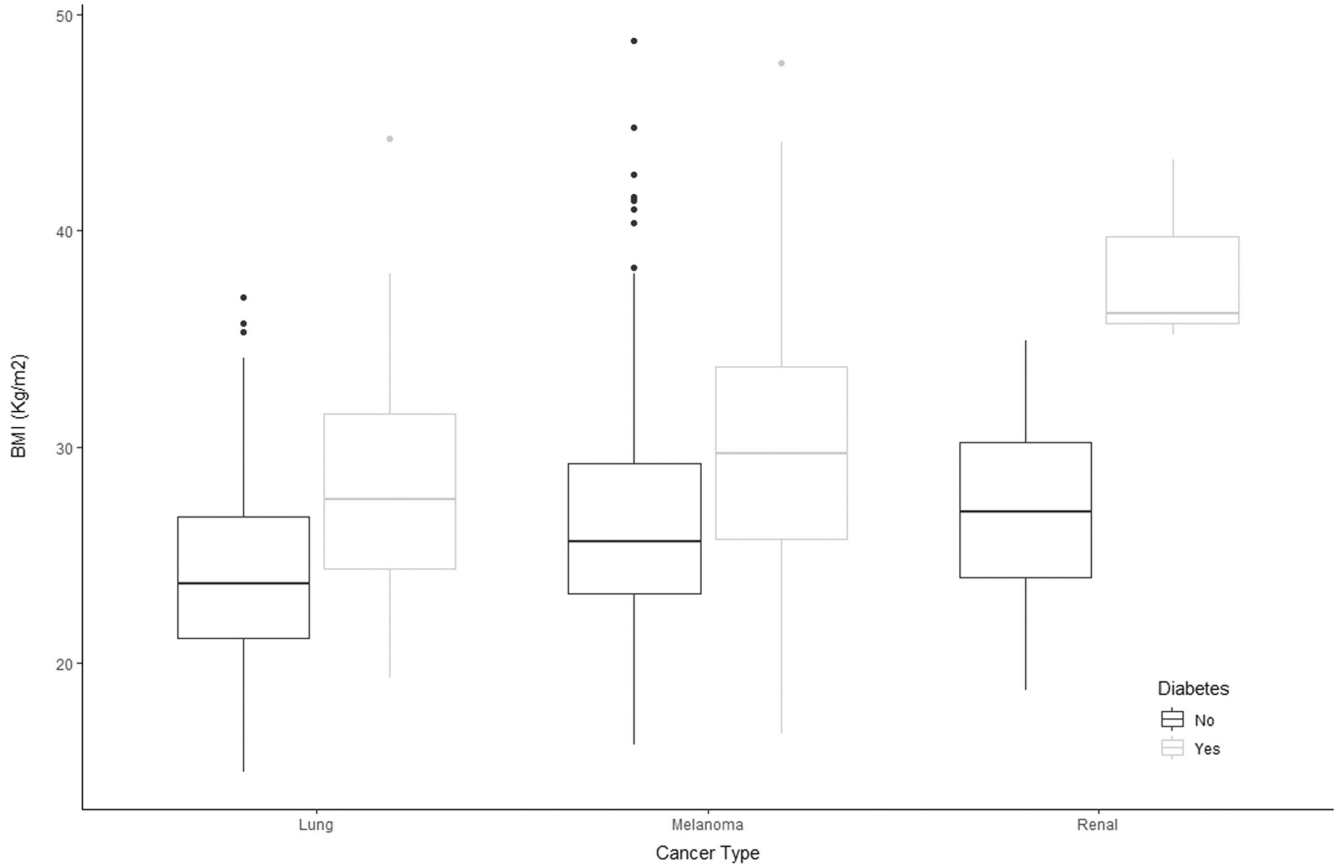

FIGURE 1 BMI in each cancer type according to diabetes status at baseline.

TABLE 2 Demographics by diabetes status.

	No diabetes ($N = 856$)	Diabetes ($N = 103$)	Total ($N = 959$)	*p* value
Age				<0.001[a]
Mean (SD)	60.4 (15.3)	67.6 (11.5)	61.2 (15.1)	
Range	15.0–92.0	12.0–86.0	12.0–92.0	
BMI				<0.001[a]
Missing	22	1	23	
Mean (SD)	25.9 (4.7)	29.3 (5.9)	26.3 (4.9)	
Range	14.9–48.8	16.7–47.8	14.9–48.8	
Glucose at start of treatment				<0.001[a]
Missing	124	7	131	
Mean (SD)	6.0 (1.3)	9.5 (4.5)	6.4 (2.3)	
Range	3.6–20.9	2.8–25.4	2.8–25.4	
Cancer type				<0.001[b]
Lung	182 (21.3%)	46 (44.7%)	228 (23.8%)	
Melanoma	649 (75.8%)	54 (52.4%)	703 (73.3%)	
Renal	25 (2.9%)	3 (2.9%)	28 (2.9%)	

[a]Linear Model ANOVA.

[b]Pearson's Chi-squared test.

In contrast eight people with renal cancer had hyperglycaemia and 20 without, giving a rate of 28.6%, which was statistically significantly higher than lung and melanoma, albeit with a small sample size.

Of the 131 people who developed hyperglycaemia on treatment, 57 had diabetes at baseline and 74 did not. Therefore, 55% people with diabetes and 8.6% people without diabetes at baseline developed hyperglycaemia ($p < 0.01$) for the comparison, RR for hyperglycaemia in diabetes compared to no-diabetes at baseline 2.05 (1.65–2.54).

Among the 74 people with new onset hyperglycaemia (i.e. those with hyperglycaemia in the first year of treatment but without diabetes at baseline), compared to those without hyperglycaemia, BMI did not statistically differ, although those with hyperglycaemia were older with a mean age of 63.9 years compared to 60.1 years in those without hyperglycaemia ($p = 0.037$). The glucose level at the start of treatment was higher in those who subsequently developed hyperglycaemia (6.9 mmol/L vs. 5.9 mmol/L, $p < 0.001$). Overall, 74% of those with hyperglycaemia received glucocorticoids, compared to 45% in those without hyperglycaemia ($p < 0.001$).

We then reviewed the medical records to determine the cause of the new onset hyperglycaemia. In this study, 56/74 people were taking glucocorticoids at the time of the onset of hyperglycaemia. None had a c-peptide or antibodies checked and were classed as having steroid induced hyperglycaemia. One person had received glucocorticoids but stopped more than a month before the onset of hyperglycaemia. We identified seven people with ICPI induced diabetes (IO induced DM) based on the above definition. All 7 required Insulin treatment and had remained on insulin at last review. Two people had undetectable c-peptide levels at presentation, but five had detectable c-peptide levels ranging from 109 to 988 pmol/L suggesting this is not a useful test to predict insulin need. Five people had GAD and Islet cell antibodies checked – only one was positive. Other autoantibodies were not checked. Two people had a new diagnosis of Type 2 diabetes after ICPI treatment, only requiring insulin during a course of glucocorticoids and off insulin at last follow-up. Two people had hyperglycaemia in the context of infection and seven had otherwise unexplained hyperglycaemia.

We then compared the demographics and presentation of those with new onset hyperglycaemia (Table 3). There was no significant difference in age, BMI or baseline glucose level according to the cause of hyperglycaemia. However, those with IO Induced DM or new onset Type 2 diabetes had a significantly higher glucose at time

TABLE 3 Demographics in new onset hyperglycaemia.

	No hyperglycaemia ($N = 782$)	Hyperglycaemia ($N = 74$)	Total ($N = 856$)	*p* value
Age				0.037[a]
Mean (SD)	60.1 (15.5)	63.9 (12.9)	60.4 (15.3)	
Range	15.0–92.0	26.0–88.0	15.0–92.0	
BMI				0.123[a]
Missing	20	2	22	
Mean (SD)	25.8 (4.7)	26.7 (4.5)	25.9 (4.7)	
Range	14.9–48.8	18.0–41.0	14.9–48.8	
Cancer_type				0.023[b]
Lung	173 (22.1%)	9 (12.2%)	182 (21.3%)	
Melanoma	589 (75.3%)	60 (81.1%)	649 (75.8%)	
Renal	20 (2.6%)	5 (6.8%)	25 (2.9%)	
Glucose at start of treatment				<0.001[a]
Missing	116	8	124	
Mean (SD)	5.9 (1.1)	6.9 (2.6)	6.0 (1.3)	
Range	3.6–10.4	3.9–20.9	3.6–20.9	
Steroid				<0.001[b]
No	432 (55.2%)	19 (25.7%)	451 (52.7%)	
Yes	350 (44.8%)	55 (74.3%)	405 (47.3%)	

[a]Linear Model ANOVA.

[b]Pearson's Chi-squared test.

TABLE 4 Characteristics of those with new onset hyperglycaemia according to cause.

	SIH (*N* = 56)	UNEX (*N* = 7)	IODM (*N* = 7)	T2DM (*N* = 2)	Infection (*N* = 2)	Total (*N* = 74)	*p* value
AGE							0.819[a]
Mean (SD)	63.0 (14.0)	67.7 (9.9)	65.1 (7.2)	68.5 (17.7)	69.5 (0.7)	63.9 (12.9)	
Range	26.0–88.0	52.0–84.0	57.0–77.0	56.0–81.0	69.0–70.0	26.0–88.0	
BMI							0.823[a]
Missing	2	0	0	0	0	2	
Mean (SD)	26.5 (4.3)	27.7 (4.4)	27.9 (7.0)	27.1 (1.7)	24.1 (5.3)	26.7 (4.5)	
Range	18.0–37.7	20.3–34.7	21.0–41.0	25.9–28.3	20.4–27.9	18.0–41.0	
Glucose at start of treatment							0.638[a]
Missing	6	0	1	0	1	8	
Mean (SD)	6.8 (2.7)	8.2 (2.7)	6.1 (1.7)	6.1 (1.4)	6.6 (NA)	6.9 (2.6)	
Range	3.9–20.9	6.3–13.3	4.6–9.2	5.1–7.1	6.6–6.6	3.9–20.9	
First elevated glucose[b]							0.002[a]
Mean (SD)	13.0 (2.1)	12.5 (0.6)	17.2 (7.5)	18.5 (6.9)	11.4 (0.1)	13.5 (3.3)	
Range	11.2–21.6	11.5–13.3	11.3–31.8	13.7–23.4	11.4–11.5	11.2–31.8	

Abbreviations: Infection, Hyperglycaemia in context of infection; IODM, Immunotherapy-Induced Diabetes; NT2DM, New Onset Type 2 Diabetes; SIH, Steroid-Induced Hyperglycaemia; UNEX, Unexplained Hyperglycaemia.

[a]Linear Model ANOVA.

[b]Six people were diagnosed with new onset hyperglycaemia outside of the window for glucose collection, so were excluded from the comparison of glucose levels.

of hyperglycaemia than those with steroid induced or unexplained hyperglycaemia (Table 4).

Finally, we looked at the variation in glucose levels in the population overall. We compared the mean of all glucose levels obtained in the 3 months prior to starting ICPI, the mean glucose in the 6 months after ICPI and the peak glucose in the 6 months after starting ICPI therapy. The mean pre glucose level was 5.91 mmol/L in those without diabetes and 10.1 mmol/L in those with diabetes. Mean glucose post treatment did not differ significantly (at 6.12 mmol/L and 9.58 mmol/L respectively). Figure 2 shows mean pre, mean post and peak post glucose levels in those with and without diabetes, according to receipt or not of glucocorticoids, and confirms that the majority of hyperglycaemia is observed in those receiving glucocorticoids.

4 | DISCUSSION

This is the largest series to systematically examine glucose changes after treatment with an immune checkpoint inhibitor. The overall rate of diabetes at baseline (at 10.7%) and hyperglycaemia during the first year after starting treatment with an ICPI (at 9.6%) are lower than those reported by Leiter et al.[21] although that study included a wider range of cancer types, and had a higher mean age and nearly 20% were in the obese range. We identified a higher rate of hyperglycaemia in those with lung and renal cancer compared to melanoma, and this study included a far higher proportion of people with melanoma than Leiter et al. Notably, both studies report significantly higher real-world rates of hyperglycaemia than in prior meta-analyses of clinical trials. This is likely to reflect a degree of under-reporting of hyperglycaemia as adverse events in clinical trials, perhaps as much of the hyperglycaemia is attributable to glucocorticoids used to manage IRAEs rather than directly to the ICPI.

In keeping with Leiter et al., we found the risk of new onset hyperglycaemia to be much higher in those with diabetes at baseline than in those without diabetes. Nevertheless, over 8% of people with no diabetes at baseline developed new onset hyperglycaemia in the following year, and while the majority of these were related to glucocorticoid use, we were able to identify a number of people matching a case definition for IO Induced DM. We confirmed previous reports showing a wide range of C-peptide levels at baseline in those with new onset insulin requiring diabetes and found a low rate of GAD and Islet Cell antibody positivity, although we did not have data on more specific autoantibodies such as IA-2A. The incidence of IO induced DM at just under 1% is in line with that reported in the literature.

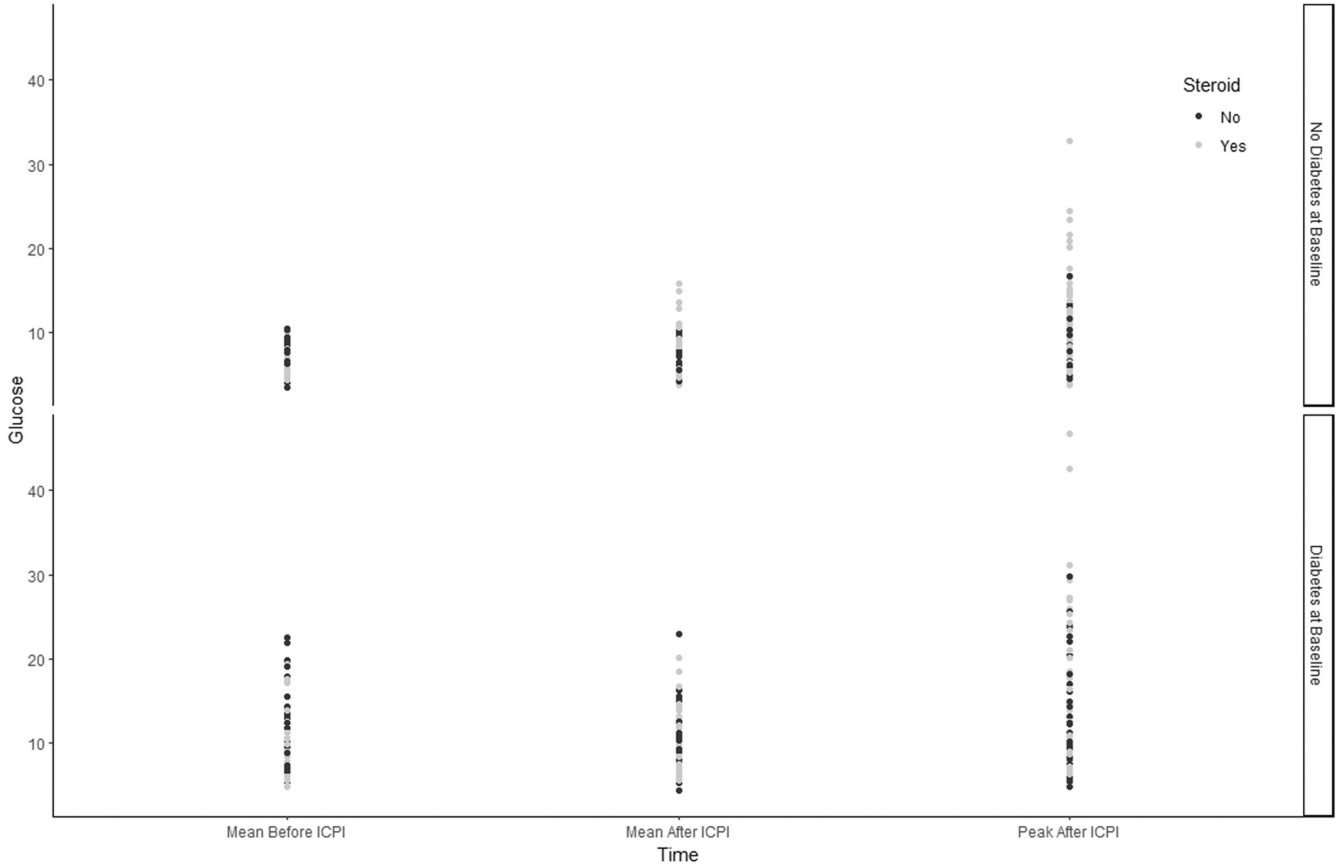

FIGURE 2 Mean glucose in the 3 months prior to starting immune checkpoint inhibitors (ICPI) therapy, the man glucose in the 6 months after ICPI, and peak glucose within 6 months of ICPI, all in mmol/L. Top panel shows those without diabetes at baseline, bottom panel those with diabetes. Black dots indicate those who did not receive systemic glucocorticoids ("Steroid") after ICPI treatment, the grey dots indicate glucose levels in those who did require steroids after treatment.

Due to the large numbers in our study, we were able to make comparisons between the different causes of new onset hyperglycaemia. There was no significant difference in BMI between the different aetiologies, and only the glucose level at time of diagnosis differed, being higher in those with IO Induced DM or new onset type 2 diabetes than in steroid induced hyperglycaemia.

There has been significant focus in the scientific literature on IO-Induced DM, with multiple case reports and case series published in the last 4 years. Clearly, a diagnosis of IO Induced DM has a major impact on an individual, requiring life-long insulin therapy. However, this data serve as an important reminder that IO Induced DM only accounts for around 10% of new onset hyperglycaemia following ICPI therapy, and careful clinical assessment of those with hyperglycaemia is required, including glucocorticoid use, and follow-up is required to ensure correct classification of the aetiology of hyperglycaemia. There is a clear need to balance the requirement for urgent insulin initiation in those who may be at risk of DKA, given the potential for fulminant diabetes,[8] while ensuring that those with other causes of hyperglycaemia are identified and either not treated with insulin or offered a trial of insulin withdrawal as appropriate (for example following glucocorticoid weaning). Equally, it is plausible that some of those who develop hyperglycaemia while taking glucocorticoids may also develop IO induced or permanent type 2 diabetes. Therefore, specialist input is vital, especially if unable to rapidly wean diabetes medication at the cessation of glucocorticoids, and there needs to be awareness of the risk of DKA when withdrawing insulin in this cohort. A limitation of this study is that we did not have access to long-term diabetes outcomes and so the final classification of cause of hyperglycaemia may be incorrect. We therefore propose an algorithm for use in Oncology settings to guide the assessment of those presenting with new onset hyperglycaemia (Figure 3). Use of such an algorithm will ensure those at high risk of DKA are started promptly on insulin.

Our study has several strengths. By using automated extracts from an EPR, we were able to include a large number of participants, with robust ascertainment of

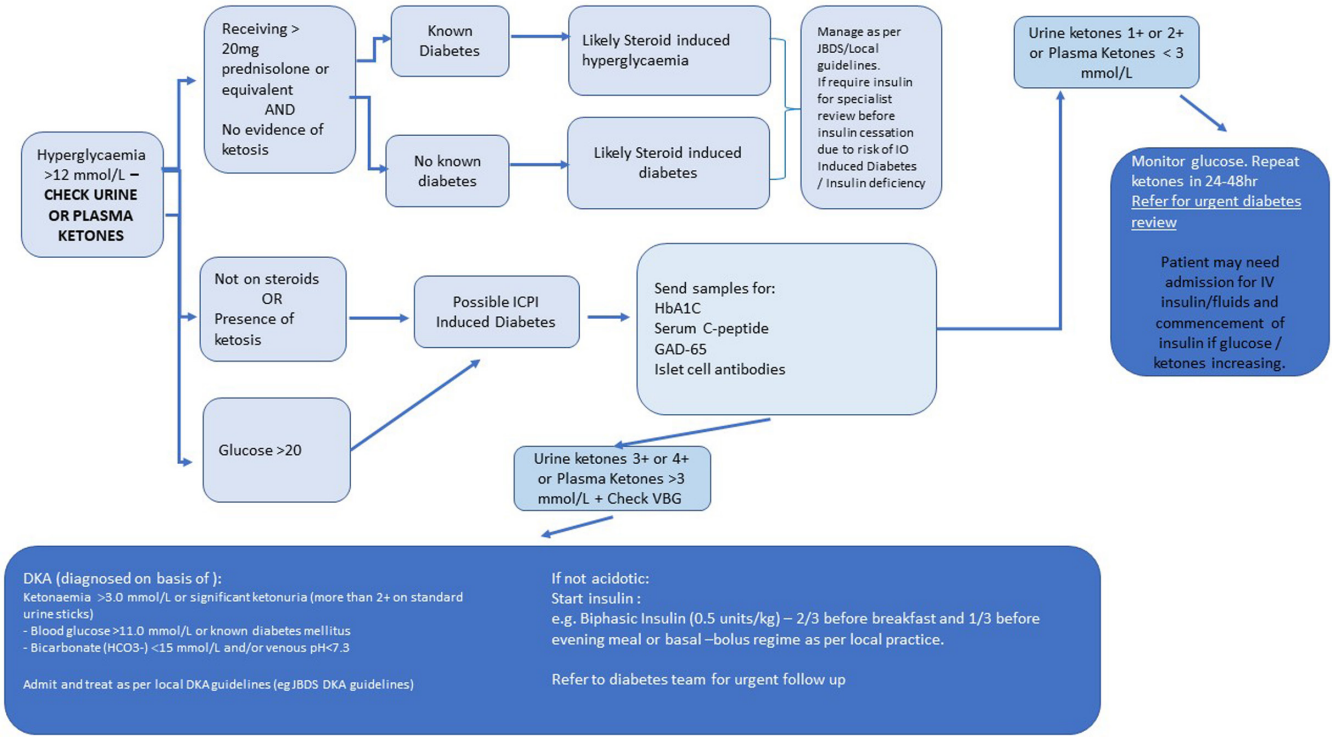

FIGURE 3 Suggested algorithm for investigation and assessment of new onset hyperglycaemia in persons treated with an ICP Inhibitor for use in Oncology Settings. Those with Steroid Induced Diabetes or Hyperglycaemia should be managed according to the JBDS Guidelines.[23,24] *At a minimum all those requiring insulin treatment, regardless of glucocorticoid use, should be referred for specialist diabetes review due to risk of ongoing insulin deficiency. 20 mg Prednisolone or equivalent has been used as threshold for high risk of steroid induced hyperglycaemia/diabetes based on JBDS Oncology guidance.[23] Individual assessment is required for those on lower doses.

their glucose data. We developed an algorithm to determine diabetes status from multiple sources of data within the electronic record. As this included pre-treatment glucose and/or HbA_{1c} levels it may have included some individuals not formally diagnosed with diabetes, but is likely to have provided a comprehensive capture of those with abnormal glycaemia prior to starting ICPI therapy. On the other hand, diabetes was only coded for those requiring an admission, meaning those with diabetes treated solely as day people, with no mention of diabetes or diabetes drugs in their clinic notes, and normal HbA_{1c} (or did not have an HbA_{1c} checked at the cancer centre) and glucose may have been misclassified as no diabetes.

In addition, the study definition of hyperglycaemia was based on random glucose readings during routine follow up. Not all participants had glucose levels checked, and we were not able to determine if glucose levels were fasting, pre-meal or post meal, or indeed the time of day. Therefore, the rate of hyperglycaemia may in fact be an under-estimate, especially among those receiving glucocorticoids, where levels are typically higher in the afternoon or early evening.[22] Given the incidence of hyperglycaemia observed, especially among those receiving glucocorticoids, consideration should be given to screening for hyperglycaemia for example with self-blood glucose monitoring. Receipt of glucocorticoids was based on prescriptions from the specialist centre – it is possible some participants may have been prescribed glucocorticoids elsewhere, which may underestimate the rate of glucocorticoid use.

In conclusion, we report rates of diabetes and hyperglycaemia among those receiving ICPI in considerable excess to that reported in clinical trials. We show that most new onset hyperglycaemia is attributable to steroid induced hyperglycaemia, but that IO induced DM requiring insulin occurs in around 1% of participants. Thus, persons receiving ICPI therapy need improved monitoring of their glucose levels, especially in those with diabetes at baseline or in receipt of glucocorticoids, and careful diabetes assessment of new onset hyperglycaemia.

AUTHOR CONTRIBUTIONS

DM, SP and JL conceived the study. BM, SM and KM collected data. SF and DM performed analysis. KM, KY and

DM developed suggested clinical guidelines. DM, SF, KM and KY wrote the final manuscript.

CONFLICT OF INTEREST STATEMENT

DM reports personal fees from BMS, personal fees from MSD, personal fees from Roche, outside the submitted work. SP reports personal fees from Amgen, AstraZeneca, Bayer, Beigene, Blueprint, BMS, Boehringer Ingelheim, Daiichi Sankyo, Guardant Health, Incyte, Janssen, Lilly, Merck Serono, MSD, Novartis, Roche, Takeda, Pfizer, Seattle Genetics, Turning Point Therapeutics, EQRx, SP also reports unpair roles with British Thoracic Oncology Group, ALK Positive UK, Lung Cancer Europe, Ruth Strauss Foundation, Mesothelioma Applied Research Foundation and ETOP-IBCSG Partners Foundation Board. JL reports Honorariums from Eisai, Novartis, Incyte, Merck, touchIME, touchEXPERTS, Pfizer, Royal College of Physicians, Cambridge Healthcare Research, Royal College of General Practitioners, VJOncology, Agence Unik, BMS, Consultancy fees from iOnctura, Apple Tree, Merck, BMS, Eisai, Debipharm, Incyte, Speaker fees from Pierre Fabre, BMS, Ipsen, Roche, EUSA Pharma, Novartis, Aptitude, AstraZeneca, GSK, Eisai, Calithera, Ultimovacs, Seagen, Merck, eCancer, Inselgruppe, Pfizer, Goldman Sachs, MSD, Institutional research support from BMS, MSD, Novartis, Pfizer, Achilles Therapeutics, Roche, Nektar Therapeutics, Covance, Immunocore, Pharmacyclics, Aveo and Grants from Achilles, BMS, MSD, Nektar, Novartis, Pfizer, Roche, Immunocore, Aveo, Pharmacyclics. Other authors report no Conflicts of Interest.

DATA AVAILABILITY STATEMENT

Individual data are not available due to limitations of study design as a service evaluation.

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