



Diabetes Update

Vol. 3 | Issue 35 | 2022

Dear Doctor,

Greetings from Micro Labs Limited. We are happy to bring you **"DIABETES UPDATE"** which contains latest and interesting news in the field of Diabetes and Endocrinology.

- External Cross-Camera Validation for Artificial Intelligence Software in Diabetic Retinopathy Diagnosis
- Improved Estimation Methods for Predicting Glycated Hemoglobin in Real-Life Conditions Using Continuous Glucose Monitoring
- Thyroid Peroxidase Antibody Elevation and Abdominal Fat Distribution in Patients with Type 2 Diabetes Mellitus
- A case report and literature review of paediatric insulinomas in a teenage female with weight loss

Should you require any specific article or medical information, please feel free to contact us at medicalservices@microlabs.in



Diabetes Update

Vol. 3 | Issue 35 | 2022

External Cross-Camera Validation for Artificial Intelligence Software in Diabetic Retinopathy Diagnosis

Diabetic retinopathy (DR) is a significant consequence of diabetes mellitus that can result in blindness. The global prevalence of DR in diabetic patients is 34.6 percent. By 2030, the global prevalence of diabetes is anticipated to climb to 10.2 percent (578 million) and 10.9 percent (700 million) by 2045, with the prevalence of DR rising in tandem. The progression of DR occurs in stages, from non-proliferative to vision-threatening proliferative (PDR). A significant pathogenic aspect of PDR is retinal neovascularization, and preventing retinal neovascularization is a study priority.¹ DR knowledge and regular DR examination at indicated time points remain unsatisfactory among these persons, owing to low compliance and limited resources in some places. As a result, developing a cost-effective DR screening programme employing fundus photography is critical for both patients and healthcare providers.² The aim of this study was to see if VeriSee DR, a deep learning image evaluation software, could be used to test for diabetic retinopathy using different colour fundus cameras (DR).

Color fundus photos of diabetes patients taken with three distinct nonmydriatic fundus cameras were recruited for validation, including 477 Topcon TRC-NW400, 459 Topcon TRC-NW8 series, and 471 Kowa nonmyd 8 series, all of which were deemed "gradable" by one ophthalmologist. The International Clinical Diabetic Retinopathy Disease Severity Scale was then utilised to diagnose referable DR using VeriSee DR. Each camera model's gradability, sensitivity, and specificity were calculated.

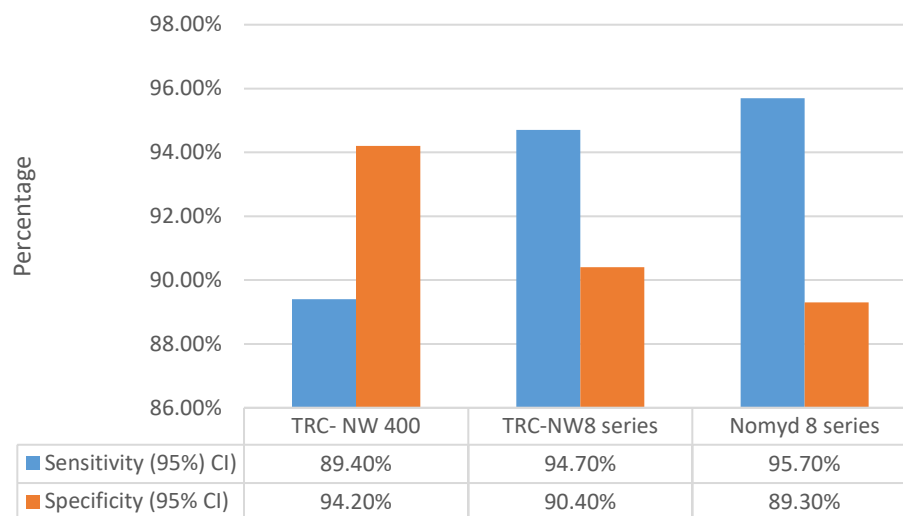
Following enrolment, 1407 fundus pictures were taken, with 477 from the TRC-NW400 series, 459 from the TRC-NW8, and 471 from the nonmyd 8 series. All of the enrolled photos (100%) were deemed gradable. The initial camera model (CR-2 series) had 95.0 percent sensitivity and 89.9 percent

Diabetes Update

Vol. 3 | Issue 35 | 2022

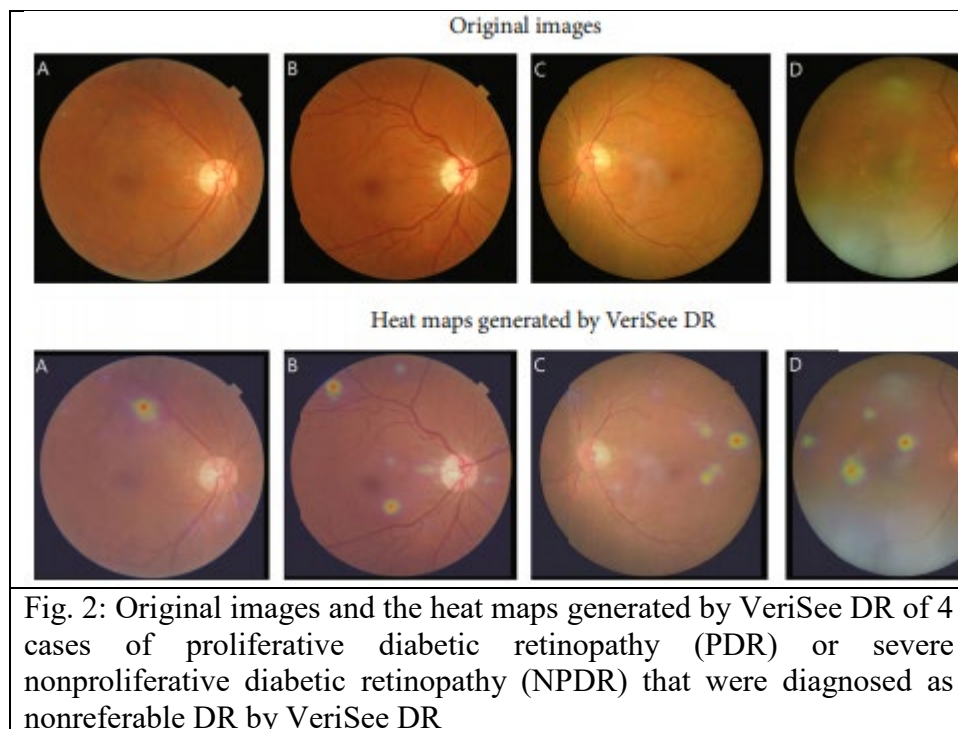
specificity, respectively. The sensitivity and specificity of the three camera models validated in this investigation varied from 89.4 percent to 95.7 percent and 89.3 percent to 94.2 percent, respectively (Figure 1). The four camera models had no significant differences in sensitivity ($p = 0.40$) or specificity ($p = 0.065$). VeriSee DR was found to be "qualified" for use in DR diagnostics with all camera models.

Fig.1: Sensitivity and specificity of VeriSee DR in diagnosing referable DR in three different camera models



Diabetes Update

Vol. 3 | Issue 35 | 2022



VeriSee DR was created with the goal of detecting referable DR. Nonreferable eyes are those that have only minimal NPDR. The previous study found that VeriSee DR showed good sensitivity and specificity in identifying any DR, including moderate NPDR, while utilising the original camera type (Canon CR-2 series).³ The sensitivity for any DR was found to be good for all three camera models in this investigation, but the specificity was lower, owing to the overdiagnosis of mild nonproliferative diabetic retinopathy (NPDR).²

Finally, the VeriSee DR automated screening system may be used with a range of colour fundus cameras (TRC-NW400, TRC-NW8 series, Kowa nonmyd 8, and Kowa nonmyd 8 s) and has 100% gradability among ophthalmologists, as well as high sensitivity and specificity for the diagnosis of referable DR.

Diabetes Update

Vol. 3 | Issue 35 | 2022

References:

1. Qiu F, Tong HJ. Inhibitory effect of maspin on neovascularization in diabetic retinopathy. *World J Diabetes*. 2021 Dec 15;12(12):2050-2057.
2. Tsai MJ, Hsieh YT, Tsai CH, Chen M, Hsieh AT, Tsai CW, Chen ML. Cross-Camera External Validation for Artificial Intelligence Software in Diagnosis of Diabetic Retinopathy. *J Diabetes Res*. 2022 Mar 9;2022:5779276.
3. Y. T. Hsieh, L. M. Chuang, Y. D. Jiang et al. Application of deep learning image assessment software VeriSee™ for diabetic retinopathy screening. *Journal of the Formosan Medical Association.*, 2021; 120 (1) 165–171.

Improved Estimation Methods for Predicting Glycated Hemoglobin in Real-Life Conditions Using Continuous Glucose Monitoring

In people with T2DM, glycosylated haemoglobin (HbA1c) is a biomarker that is routinely used to diagnose diabetes, monitor glycemic control, and guide therapy.¹ In turn, real-time continuous glucose monitoring (RT-CGM) provides for the collection of a large amount of glucose data, which may be used to estimate HbA1c without the need for laboratory testing.² The use of continuous glucose monitoring (CGM) in hospitalised patients has shown to be superior to standard point-of-care (POC) capillary blood glucose testing in terms of preventing severe hypoglycemia and hyperglycemia, as well as decreasing the burden of care on nursing staff. Davis and colleagues have published the largest clinical trial to date on the accuracy of CGM use in a broad sample of non-critically ill diabetic patients.³ A number of research looked into the relationship between estimated HbA1c from CGM, also known as eA1C or glucose management indicator (GMI), and average glucose readings. The degrees of freedom in the eA1C evaluation approach

Diabetes Update

Vol. 3 | Issue 35 | 2022

are investigated in this research in order to eliminate differences with HbA1c assays.²

The study enlisted the participation of 33 Caucasian patients from northwestern Italy. The use of prescribed commercial G6 (Dexcom, San Diego, CA) devices, which were fully reimbursable and repaid by the Italian National Health System, as well as procedures for uploading CGM data to the DIASEND (Glooko, Mountain View, CA) and CLARITY (Dexcom, San Diego, CA) websites, were explained to patients. Because the study was entirely observational, subjects participation had no bearing on the care team's conduct or decisions, and patients were free to handle their devices on a daily basis.

Bland-Altman (BA) plots reveal that, in addition to a good mean interstitial glucose (MIG) to HbA1c regression equation, clever interpolation to patch missing data and a wise choice of interstitial glucose (IG) weighting function increase HbA1c estimation quality. The improvement is confirmed by a decrease in the BA plot-related variance of differences in comparison to the gold standard. Wilcoxon signed-rank tests on the bias-compensated mean squared error (MSE) compared to traditional MIG-based approaches reveal that the improvement is statistically significant ($P = .0179$).

Diabetes Update

Vol. 3 | Issue 35 | 2022

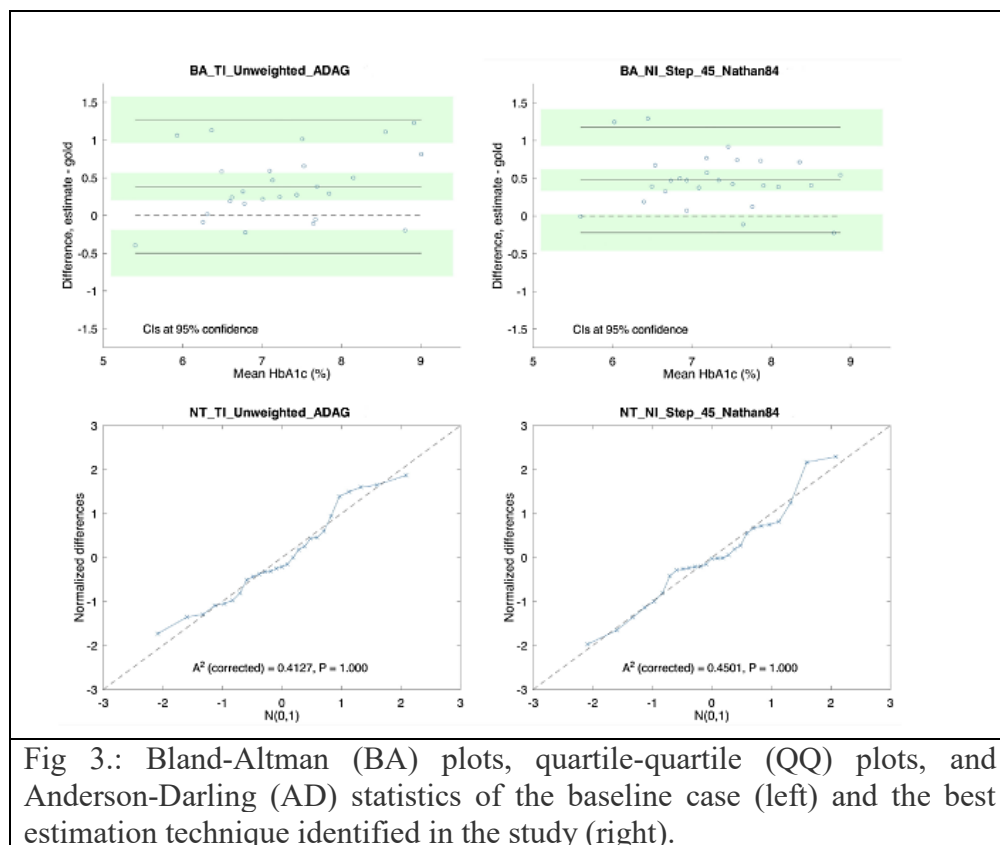


Fig 3.: Bland-Altman (BA) plots, quartile-quartile (QQ) plots, and Anderson-Darling (AD) statistics of the baseline case (left) and the best estimation technique identified in the study (right).

The mismatch with respect to the normal distribution is small ($P = 1.000$) according to the Anderson-Darling (AD) test. The AD A^2 test statistics were adjusted to account for the short sample size. Figure depicts how the HbA1c prediction error is distributed for the sample patients using TI Unweighted ADAG (baseline) and the best methods identified in the first and second steps of the study, NI Step 45 ADAG and NI Step 45 Nathan84, to highlight how the estimation method affects the discrepancy between eA1c and HbA1c. With respect to the baseline, the best estimation approach found in this study (yellow bars) doubled the number of patients whose prediction error is in the $[0.125, +0.125]$ percent band (purple bars). Except for

Diabetes Update

Vol. 3 | Issue 35 | 2022

a minor rise (from 3 to 5 patients) in the $[0.125, 0.375]$ range, the number of patients with a larger prediction error dropped or remained steady.

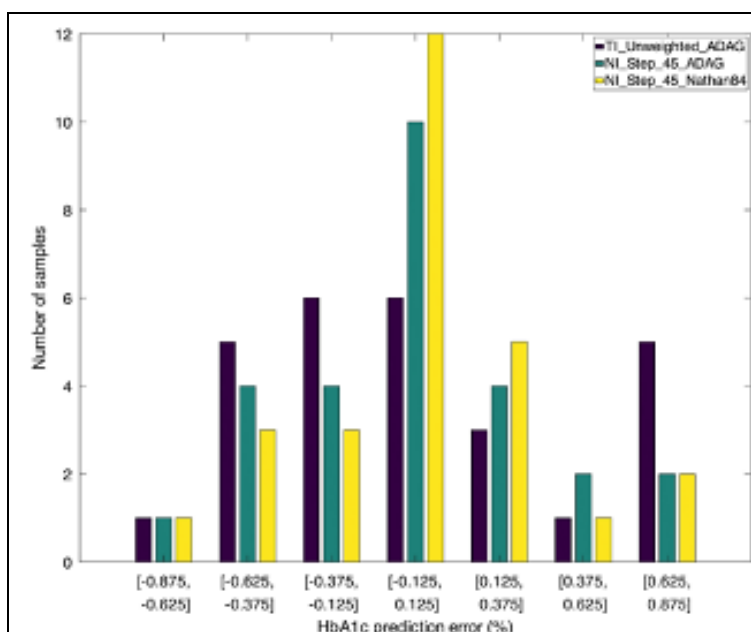


Fig. 4: Distribution of the HbA1c prediction error of the 3 main estimation techniques considered in the study for the sample patients.

As proposed by Vettoretti et al, systematic errors in CGM data caused by imperfect sensor calibration can be modelled as time-variant additive and multiplicative error terms of $ig(t)$, whose effect on HbA1c estimation can in theory be assessed by incorporating these same terms in the mean interstitial glucose (MIG) equations previously presented.⁴

Improved HbA1c estimation approaches result in superior HbA1c prediction quality as compared to those based solely on MIG, allowing diabetologists with quick but still somewhat accurate

Diabetes Update

Vol. 3 | Issue 35 | 2022

feedback. They reduce the discrepancies described in the literature and, with future development, could be a viable complement/alternative to HbA1c tests.

Reference:

1. Jansson AK, Chan LX, Lubans DR, Duncan MJ, Plotnikoff RC. Effect of resistance training on HbA1c in adults with type 2 diabetes mellitus and the moderating effect of changes in muscular strength: a systematic review and meta-analysis. *BMJ Open Diabetes Res Care*. 2022 Mar;10(2):e002595.
2. Valenzano M, Cibrario Bertolotti I, Grassi G, Broglio F, Valenzano A. Predicting Glycated Hemoglobin Through Continuous Glucose Monitoring in Real-Life Conditions: Improved Estimation Methods. *J Diabetes Sci Technol*. 2022 Mar 14:19322968221081556.
3. weeney AT, et al. Use of a Continuous Glucose Monitoring System in High Risk Hospitalized Non-critically ill Patients with Diabetes after Cardiac Surgery and during their Transition of Care from the Intensive Care Unit during Covid-19-A Pilot Study. *Endocr Pract*. 2022 Mar 8:S1530-891X(22)00072-6.
4. Vettoretti M, et al. Modeling the error of factory-calibrated continuous glucose monitoring sensors: application to Dexcom G6 sensor data. 41st Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC). 2019;2019:750-753

Thyroid Peroxidase Antibody Elevation and Abdominal Fat Distribution in Patients with Type 2 Diabetes Mellitus

Obesity has been on the rise in recent decades, according to a plethora of evidence. Metabolic disorders (insulin resistance, type 2 diabetes mellitus, and nonalcoholic fatty liver disease), immune-mediated diseases, and several kinds of cancer are among the comorbidities linked to obesity. At the same time, there has been an increase in the prevalence of autoimmune illnesses, including thyroid autoimmunity¹. Autoantibodies against thyroid antigens, such as thyroid peroxidase antibody (TPOAb), thyroglobulin antibody (TGAb), and TSH receptor antibody, describe autoimmune thyroid disorders (AITDs) (TRAb). Thyroid autoantibodies are commonly

Diabetes Update

Vol. 3 | Issue 35 | 2022

high in patients with T1DM, according to previous research, and are thought to be linked to autoimmune and inflammatory pathways. Thyroid autoantibodies, on the other hand, have been found to be more common in the T2DM population, such as in individuals with T2DM and NAFLD, in recent research. ²The researchers looked at the link between a high titer of thyroid peroxidase antibody (TPOAb) and visceral fat area in T2DM patients.

This study included 390 T2DM patients who met the admission requirements and were admitted to the National Metabolic Management Center (MMC) at the Zhejiang Provincial People's Hospital between April and December 2020. On the basis of visceral obesity, the subjects were separated into two groups. Blood tests were used to assess thyroid function, thyroid related antibodies, and other metabolic markers. Bioelectrical impedance analysis was used to determine the visceral fat area (VFA) and the subcutaneous fat area (SFA).

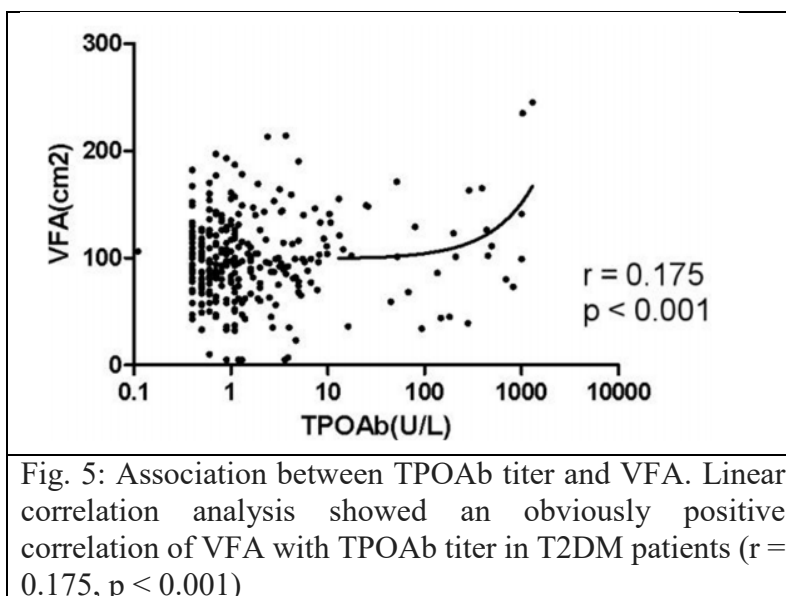
There were 185 people in the study who had visceral obesity (47.4%). TPOAb positivity was considerably greater in T2DM patients with visceral obesity (12.97 percent versus 5.37 percent, $p = 0.01$) than in T2DM patients without visceral obesity. Thyroid-stimulating hormone (TSH) and free triiodothyronine (FT3) were both considerably greater in T2DM individuals with visceral obesity ($p < 0.05$) (Table 1). TPOAb titer was found to be substantially linked with visceral fat area ($r = 0.175$, $p < 0.01$) (Figure 5). TPOAb positivity was linked to an increased risk of visceral obesity in a binary logistic analysis [(OR) 4.258, 95 percent confidence interval (CI) 1.594, 11.375, $p = 0.004$].

Diabetes Update

Vol. 3 | Issue 35 | 2022

Variables	Visceral Obesity (n = 185)	Normal (n = 205)	P value
TPOAb(+), n (%)	24(12.97%)	11(5.37%)	0.009*
TGAb(+), n (%)	12(6.49%)	9(4.39%)	0.360
TPOAb and TGAb(+), n (%)	9(4.87%)	4(1.95%)	0.154
TSH	1.90(0.94-2.86)	1.70(0.77-2.63)	0.032*
FT3	3.17(2.74-3.61)	3.05(2.64-3.46)	0.004*
FT4	9.50(8.04-10.96)	9.38(7.70-11.06)	0.443

Table 1: Comparison of Thyroid Indicators of T2DM Patients with and without Visceral Obesity



It has previously been observed that T1DM patients had a significant frequency of autoimmune thyroid illness. However, this is a little researched area in T2DM, particularly in T2DM with obesity. The current study is the

Diabetes Update

Vol. 3 | Issue 35 | 2022

first to look at the link between visceral obesity and thyroid autoimmunity in a T2DM-affected Chinese population. In participants with T2DM and adequate thyroid function, the study found an independently positive link between visceral adiposity and thyroid autoimmunity. Autoimmune thyroid disease is more frequent in people with T2DM and NAFLD, according to Wang C et al. The results reveal that the positive rate of TPOAb in the T2DM combined visceral obesity group was greater than the T2DM only group, suggesting that elevated TPOAb titer is a predictor of autoimmune development in T2DM with NAFLD.³

TPOAb-positive patients with T2DM are more likely to have visceral obesity, which has some effects on visceral obesity that are independent of thyroid function. This implies that a high TPOAb titer in T2DM patients is a predictor of visceral adiposity.

Reference:

1. Baranowska-Bik A, Bik W. The Association of Obesity with Autoimmune Thyroiditis and Thyroid Function-Possible Mechanisms of Bilateral Interaction. *Int J Endocrinol*. 2020 Dec 14;2020:8894792.
2. Hu Y, Zheng J, Ye X, Song Y, Wu X. Association Between Elevated Thyroid Peroxidase Antibody and Abdominal Fat Distribution in Patients with Type 2 Diabetes Mellitus. *Diabetes Metab Syndr Obes*. 2022 Mar 17;15:863-871.
3. Wang C, Niu Q, Lv H, Li Q, Ma Y, Tan J, Liu C. Elevated TPOAb is a Strong Predictor of Autoimmune Development in Patients of Type 2 Diabetes Mellitus and Non-Alcoholic Fatty Liver Disease: A Case-Control Study. *Diabetes Metab Syndr Obes*. 2020 Nov 16;13:4369-4378.

A case report and literature review of paediatric insulinomas in a teenage female with weight loss

Insulinomas are rare insulin-secreting pancreatic neuroendocrine tumours (pNETs) with a 4 case per million annual incidences. Because of independent insulin secretion, most insulinomas are sporadic, solitary, and benign, yet they are associated with life-threatening hypoglycemia. Insulinomas are cancerous in about ten percent of cases, and 4 percent to

Diabetes Update

Vol. 3 | Issue 35 | 2022

seven percent are linked to multiple endocrine neoplasia syndrome type I. Insulinoma is frequently misdiagnosed due to its deceptive, vague symptoms that resemble other conditions such as mental illness.¹ Due to the increased amount of carbs taken to prevent or counter hypoglycemia, an individual with an insulinoma may present with increased body weight. An adolescent female presented with hypoglycemia due to an insulinoma as part of the multiple endocrine neoplasia type 1 syndrome, according to this study (MEN 1).²

Case Presentation:

Syncopal episodes, nausea, exhaustion, diplopia, and weight loss were brought to local emergency department (ED) by a previously healthy 14-year-old female of South Asian heritage. There was no history of hypoglycemia. Her blood glucose (BG) was lower than usual, but there was no diagnosis. She had low blood sugar readings around twice a week throughout the first month of BG monitoring. She performed a minimally invasive pancreatic enucleation surgery after completing her biochemical and imaging evaluations and verifying that her blood sugar level remained stable. She had a good recovery with no issues after the procedure. Anti-insulin antibody staining of the pancreatic material ruled out other functional (glucagonoma, gastrinoma, somatostatinoma, or vasointestinal peptide tumour (VIPoma)) and non-functioning tumours.(Figure 6)

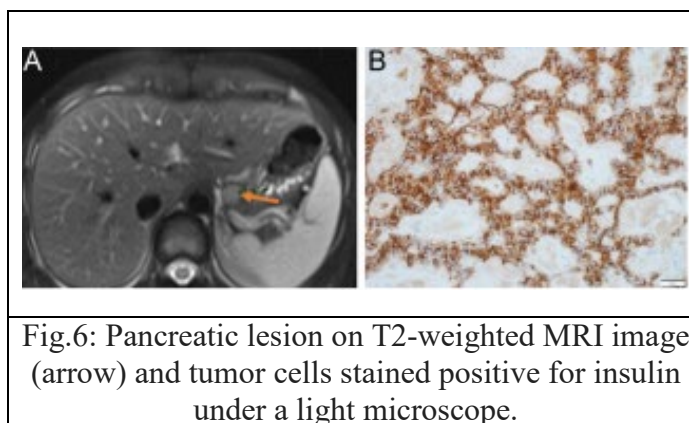


Fig.6: Pancreatic lesion on T2-weighted MRI image (arrow) and tumor cells stained positive for insulin under a light microscope.

Diabetes Update

Vol. 3 | Issue 35 | 2022

Fasting (80–99 mg/dL) and 2-hour post-prandial (80–140 mg/dL) capillary BG levels remained normal within 24 hours of surgery. A microadenoma was discovered on an MRI of the brain, which showed a focused area of enhancement along the right side of the pituitary gland (Figure 7). A heterozygous genetic mutation in the *menin* gene (C.35 C >T) was discovered during genetic testing for the *MEN1* gene. She denied galactorrhea, bone pain, any hypoglycemic symptoms nearly ten months after her initial presentation, while still claiming oligomenorrhea. Her calcium levels (11.8 mg/dL), PTH levels (86.8 pg/mL), and prolactin levels (202 ng/dL) all rose. She had a partial parathyroidectomy to lower her parathyroid hormone (PTH) and calcium levels, and she started taking cabergoline to lower her prolactin output. Her calcium and PTH levels improved within two months, and her menstrual cycles were more regular.

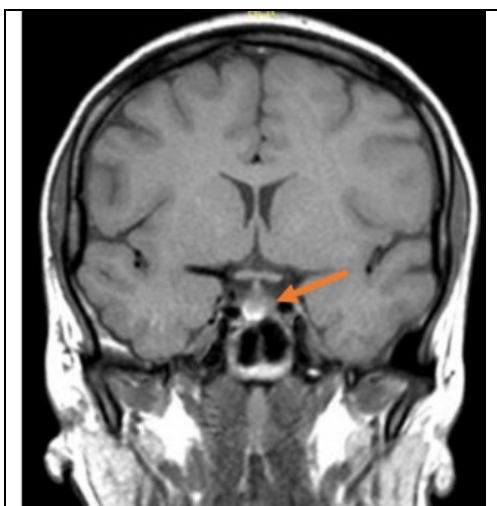


Fig.7: Coronal section of the MRI brain showing a pituitary microadenoma just above the Sella turcica

Diabetes Update

Vol. 3 | Issue 35 | 2022

Imaging investigations of the abdomen, such as ultrasound, CT, and magnetic resonance image (MRI), may help pinpoint the tumour when an insulinoma has been diagnosed. Enucleation of the tumour is the preferred treatment if an insulinoma is discovered.³ The lack of appetite and weight loss in this patient were unusual for an insulinoma. It was only after further discussion with the patient about her eating habits that it became clear that she had a restrictive eating pattern and was afraid of gaining weight. This led to a verified diagnosis of anorexia nervosa, which explained why she hadn't gained weight while having an insulinoma. Only 32 other examples involving a child or adolescent with an insulinoma were found in a survey of the literature over the last 50 years. Weight loss (14 cases), hunger (8 cases), and MEN1 (27 cases) were all mentioned in addition to our case. One case (case #2) involved a malignant insulinoma, and seven cases were linked to MEN1.² Unlike the patient, who reported substantial hunger, the clinicians were only able to find one other case in which a patient came with hypoglycemia and weight loss (case #21).⁴

Insulinomas in children and adolescents, like those in adults, are associated with increased carbohydrate intake and considerable weight gain. Any child or adolescent presenting with hypoglycemia should have a full nutritional, psychiatric, and family history taken.

References:

1. Alyusuf EY, Ekhzaimy AA, Rivera JA. Radiofrequency Ablation as a Primary Therapy for Benign Functioning Insulinoma. *AACE Clin Case Rep*. 2020 Dec 28;7(2):153-157.
2. Gupta P, Loechner K, Patterson BC, Felner E. Insulinoma in an adolescent female with weight loss: a case report and literature review on pediatric insulinomas. *Endocrinol Diabetes Metab Case Rep*. 2022 Mar 1;2022:21-0206.
3. van Beek DJ, Nell S, Verkooijen HM, Borel Rinkes IHM, Valk GD; (on behalf of the DutchMEN study group), Vriens MR; International MEN1 Insulinoma Study Group. Surgery for multiple endocrine neoplasia type 1-related insulinoma: long-term outcomes in a large international cohort. *Br J Surg*. 2020 Oct;107(11):1489-1499.



Diabetes Update

Vol. 3 | Issue 35 | 2022

4. Miron I, Diaconescu S, Aprodu G, Ioniuc I, Diaconescu MR, Miron L. Diagnostic Difficulties in a Pediatric Insulinoma: A Case Report. Medicine (Baltimore). 2016 Mar;95(11):e3045.

This scientific input is prepared from the Department of Medical Services, an initiative of M/s Micro Labs Limited under the aegis of Micro Knowledge Academy. The information contained herein is for education purpose only. The content is developed by compiling information from various authentic and published literatures. Although great care has been taken to assure the accuracy of the publication, M/s Micro Labs Limited shall not be responsible or in any way liable for any inaccuracy, errors, or omissions resulting from negligence or otherwise howsoever or any consequences arising there from. In spite of best efforts, the information in this publication may become outdated over time. M/s Micro Labs Limited shall not be responsible in any manner whatsoever, for any action taken, opinions expressed, advice rendered or accepted, any direct, incidental, special or consequential loss and damage caused on the basis of any material or information presented in this publication / update