**Diagnosing and Classifying Diabetes for Primary care Transcript**

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0:00 **Chair:** Good evening everyone, and thank you for joining tonight's webinar on diagnosis of diabetes. Really pleased to introduce Vinay Eligar who's a Diabetologist in Cardiff & Vale. And this is going to be part of a diabetic series that we're planning to put on and record over the next six months. We've got diagnosis of diabetes today and then we're going to follow with pre-diabetes and control, diabetes remission once you've been diagnosed, then managing diabetes, concentrating on Type 2 for general practise and then also touching on renal disease, foot problems and insulin as well. So hopefully we're going to build up a nice series that we can then put together into a package that will be available on our web pages. So without further ado, we've got about an hour today. We've got some presentations, we've got some case studies, and we'll take your questions at the end. So Vinay over to you.

1:08 **Speaker:** Good evening everyone, and thanks Nimish for inviting me to present here. Quite honoured to be here. So the topic I was given was diabetes diagnosis and classification, which sounds quite a straightforward topic, which is usually straightforward most times. But at times we may have to divulge a little bit. And you can come up with some surprising diagnosis at times.

1:45 **Speaker:** So it's more like a precision medicine or precision diagnosis, individualised treatment options for patients. So that's the direction we are looking at, especially in terms of managing diabetes, because not everybody is on the same path, the same treatment, or has the same requirements of intensification.

2:11 **Speaker:** So precision diagnosis usually comes from epidemiological evaluation, what is the prevalence of a particular condition, what could be other rare types that could be thought of probability based upon clinical features, which is probably the most important aspect for all of us during our clinical times. And how can we use the diagnostic testing to aid and come to the right diagnosis and classify your patients into the right box if you want to say or into the right category?

2:48 **Speaker:** So in general, diabetes could be because of various reasons and the majority, what we see is the Type 2 beta cell failure being the cause for it. So the presentation is mostly talking about patients who have high BMI central obesity lifestyles which could be contributing. More often now rather than just trying to treat something in the early days of Type 2 diabetes. We should also think about reversal and remission that is taking more ground now and condition, because of the different various antibodies and their phenotype could be slightly different to Type 2. So when should we think of Type 1 diagnosis? This would probably be the most of my slides and explaining why that could be. And the other group would be genetic diabetes, which unless we look for it we won’t find it. I’d like to think of secondary diabetes and the rarest types are always rare. So the common things are always common. So we probably will be holding around these three topics, gestational diabetes I'm not going to touch upon that because it's predominantly managed in the antenatal unit. The only time the input, which is quite vital and sometimes missing is And there's no pathways built around how we can capture these patients, because these are the ones who have a high risk to develop Type 2 diabetes in the future.

4:33 **Speaker:** So diagnosis of diabetes Type 2 is pretty straightforward you might think, because patients either come with fasting hypoglycaemia and postprandial hypoglycaemia. And the QOF values are, this is asked for. The last slide was basically looking at different Types of diabetes and which one we’ll be covering most, it would be Type 2, Type 1 and genetic diabetes predominantly. So the diagnosis of Type 2 is based upon the ADA guidance, which will go further through a little bit more. Basically, we can use a fasting plasma glucose. If you are able to get a fasting, it would always be beneficial to do a HBA1c at the same time, because two tests could be done, two different tests to diagnose it in one go.

5:29 Speaker: So when we use HBA1c as a marker or a diagnostic tool, we should be also be quite open to the fact that it’s not always reliable and haemoglobin variants, and especially in Afro Caribbean population where they may carry a sickle cell trait, the variant can affect the HBA1c values, patients who have anaemia or those who are on haemodialysis, where there's weekly turnover of red blood cells, Epoetin therapy, which could add to complexities of HBA1c because Epoetin can stimulate bone marrow and is increased turnover of red cells. Most recent blood transfusions, pregnancy, G6PD deficiency or treatments, especially protease inhibitors with HIV treatments. So just as a background, are we always getting the right diagnosis just because we are doing HBA1c which is so easy to do. But the commonest ones would be, I would say, anaemia. Make sure your patients are not anaemic when you read the HBA1c, have an FBC value with it.

6:44 **Speaker:** So how can we confirm Type 2 diabetes? You can either do HBA1c two different tests and a value of more than 48 mmol/mol, so confirmatory test a couple of weeks after the first one is usually helpful. If we can manage to get fasting plasma glucose more than 7 and HBA1c of 48 mmols on the same sample, then it is in one go. Or patients with symptoms who have random blood glucose of more than 11 and they have all the osmotic symptoms or symptoms of hypoglycaemia. You don't need any further tests that is diagnostic as well. But we always want to do a HBA1c to look at chronicity of hypoglycaemia in these patients. So as you can see we’ll add value there.

7:38 **Speaker:** But sometimes when we go looking for diabetes, we might find patients with pre diabetes, which is quite common, especially as nobody can become Type 2 diabetes patients in one day. So there will be a phase where they go through fasting hypoglycaemia or impaired glucose tolerance or a HBA1c value if you are doing one as a one stop test HBA1c between 42 to 47 mmol/mol is considered to be pre-diabetes. I’ve over written here because this was from the American guidelines and they use a much lower HBA1c of 39-47 as pre-diabetes. But I know some of the GP surgeries where they actually did some pilot studies to recognise these three diabetes patients. But what do we do after diagnosing them? Do we have enough support because pharmacological treatment may not be the mainstay all the time, but at least diagnosing them would give us a chance to make lifestyle modifications and consider a reversal of the process.

8:47 **Speaker:** So who should we test for diabetes or prediabetes, especially Type 2 diabetes, high risk patient groups. When I say high risk groups, Asian nations or South Asians fall under the high risk category and a BMI of more than 23 should be considered as a high risk because BMI is our ethnicity specific. In Caucasians BMI of more than 25 kilograms with following risk factors like first degree relatives, high risk ethnicities, which we discussed, history of cardiovascular disease, hypertension, hyperglycaemia and women with polycystic ovaries or women with a previous history of gestational diabetes, they would all be high risk patients to develop Type 2 diabetes.

9:37 **Speaker:** So diagnosing Type 2 diabetes is pretty straightforward, but which test to use? You may want to combine FPG (fasting plasma glucose) with HbA1C might be a one-step way of doing it in one sitting because only one sample has to be drawn.

10:06 **Speaker:** So the next commonest one we would like to not miss at all is Type 1 diabetes. And if you see the poster on the right side, which we are all very familiar with, these from Diabetes UK, to say that patients with osmotic symptoms, which is polyuria, polydipsia, feeling tired, excessive sleep and losing weight. These form the basis to say that somebody is insulinopenic and when they have insulin deficiency develop all the symptoms because they are not able to utilise the glucose. So the glycosuria further drives water loss and they’re losing weight because they are using up their muscle mass and fat mass to provide energy for them. But nobody would become Type 1 in one day, again it is a progressive condition. Sometimes we can recognise it much earlier, so currently we usually stage it as stage one, stage two, stage three. Stage three is when they have florid clinical symptoms and we present with all the osmotic features and are almost in DKA situation and we pick them up in the hospital. Stage one is difficult to pick unless we know that there's a family member with autoimmune condition or Type 1 diabetes and we have gone ahead to actively screen for them. So if somebody with autoimmune condition, maybe other autoimmune conditions like autoimmune hypothyroidism or Addison's disease, those would be the patients who may actually develop other autoimmune conditions as well. So screening might be useful there, but this is something that we rarely can do or can think of because they don't come seeking advice. But keeping an open mind in these patients to think of Type 1 diabetes, if they have other conditions, would be a good start.

12:04 **Speaker:** So the Type 1 diabetes can spread across the whole of the age group, as you can see, so this slide shows what antibodies are positive in Type 1 diabetes, which is GAD antibodies, islet cell antibodies, zinc transport 8 antibodies, which we hardly do invase. But it's one of the antibodies which should be done as well. So if they have all the three antibodies positive, the likelihood that they will develop Type 1 diabetes earlier in the life is much higher because they have got more than one type of antibodies working against the pancreatic islet cells or insulin packaging and releasing phenomena. So they do develop Type 1 diabetes earlier. If they have less a number of antibodies or just one of them, they can develop it later in the life. It also depends upon the titus of the antibodies. So if they have low titter or one antibody only, that's when we pick up patients who present us like a late onset autoimmune diabetes or latent onset autoimmune diabetes.

So these are the patients in which we pick up later in life. And the phenotype is quite slightly different compared to Type 2. And they will have also osmotic symptoms that could be like a clinical feature, osmotic symptoms with weight loss. We should think of Type 1 like presentation or autoimmune disease.

13:37 **Speaker:** The next important one, which we can consider in our clinical practice, is somebody who is not fitting into this phenotype of Type 1 or Type 2, because the presentation is very odd. The person may be in second or third decade with mild hypoglycaemias, not typical of a Type 1 presentation, not so much of osmotic symptoms, not so much of weight gain, not simply obese, but could have significant family history of diabetes diagnosed in second or third decade, especially in the first degree relatives. And because they’re of the phenotype, we invariably check their antibodies and they’re negative. And these are the patients we should think about genetic diseases, especially if they have a good going family history and the most common genetic diabetes, what is commonly known as maturity onset diabetes of young, the three different mutations and the commonest one is HNF 1Alfa mutation, which accounts for about sixty five percent. And they usually present the postprandial hyperglycaemia. That means they may have normal fasting plasma glucose if you do the HBA1c in the diabetes range, but not severely high and bedside clinical examination or immediate tests, one of the tests which we usually do, is we urine dip them and see if they have glucosuria ketonuria, and they usually have glucosuria in comparison to HNF 4Alfa, which is less than 10 percent of patients. They have usually a normal renal glucose tolerance. But they also have post prandial hyperglycaemia. The one which is about 10 to 31 percent is fasting hyperglycaemia only, these patients with glucokinase mutation don't have postprandial hyperglycaemia. If you do their oral glucose tolerance test, you'll only notice that they have mildly higher fasting glucose, their insulin release mechanism is only set slightly higher than the normal. So they will have a fasting hyperglycaemia, but never postprandial hyperglycaemia and the management can be quite/ slightly different here. That's the reason we need to get to these patients and diagnose them because the management can be quite different and quite rewarding, because patients may not be started on the medications that are not needed, especially insulin, which can be for life once started.

16:04 **Speaker:** There is a very good website, as you know, Exeter is a pioneer centre for all the types of genetic diabetes diagnosis. They have a very nice calculator MODY Calculator, which you can use. I put up the Web address on the top here, and it gives you a probability whether a person may be having MODY or not, and based upon the probability you can refer them to the secondary care. Or there used to be, I don't know what has happened now. We used to have a nurse who used to collect all information and liaise directly with the Exeter team, but you can always send these patients, if you think that probability is higher to the Secondary care straight away.

16:50 **Speaker:** So about two years ago, a group in Scandinavian country looked at around nine thousand patients and tried to see if they can come out with a normal subgroup of classification for diabetes.

This is no way we are going to use it in clinical practice. But just to say that most of their five groups that they made, fall into clinically they're quite relevant, because you’ll either see a very severe autoimmune Type 1 diabetes or insulin deficient but GAD negative patients. You'll see severe insulin deficient diabetes patients or obesity related diabetes or mild age-related diabetes that is in older patients, which usually has very mild. They probably need very small doses of DPP-4 inhibitor or they're well managing on gliclizide. But this is something that was interesting when the paper came out. But it has not caught up with the clinical practise because it does not help actually in categorising patients so much stringently into each category in one go. So the diagnosis of diabetes could change.

18:07 **Speaker:** So you should always keep an open mind, which especially in clinical practise, sometimes what diagnosis made about 20 years ago may not hold true today. And more than often see one or two of such cases, even in secondary care practise once every six months or two or three patients in a year where we have thought about it differently and found that they were not actually Type 1 diabetes patients. So when should we think outside the box and think that, oh I'm doing something unusual here? It doesn't look like a straightforward Type 2 diabetes. So clinical features not correlating with biochemical findings. Onset and presentation versus incidental finding, somebody presenting with symptoms, that means they have progressive beta cell loss or dysfunction going on versus somebody who we find incidentally, which could be that we found them early. But we should also think about do they fit into that phenotype or do they fit into the antibody profile or not? Of course, when you are using steroids or some of the diabetes induced medications, we have to think about these aspects as well, whether stopping these medications or withdrawing them could change the outcome. Very rarely you can come across a patient with pancreatic exocrine dysfunction who eventually also develop some endocrine dysfunction. So keeping an open mind, because these are the patients who need insulin rather than all agents.

19:41 **Speaker:** So having gone through a few of the diagnostic criteria’s, I just present a few cases which might tickle us and say that, OK, we should have thought about differently. So here we have a 55 year old male. These are all secondary care cases. So excuse me if I am actually showing you something that you don't deal on a regular basis, but these patients we most of the times we manage together. So it might be useful. So he came in with all the features of nausea, vomiting, like a DKA picture. His BMI was 26 kilograms per metre square, quite gluco toxic blood ketones were 3.5. So he was managed as DKA as you can also see that he was in acute kidney injury, which is not uncommon to see when somebody is in DKA because they will be volume deplete, they'll have pre-renal failure, which could have contributed to the slightly more metabolic picture here. He was managed on DKA protocol and strangely he was started on 20 units of mixed insulin because we generally tend to like using basal bolus insulin in Type 1 diabetes because he was managed as Type 1 here. But there is no mistaking imagining him as a DKA because he presented as DKA.

21:06 **Speaker:** So what happened, after one year of follow up he was seen in the clinic. He had an autoimmune profile which was negative, and his insulin was managed, still on insulin twice daily and his HBA1c dropped from 65 which was not a significantly high HBA1c when he came in to 38 mmol now. And he was fine.

21:29 **Speaker:** And looking at his glucose monitoring, you can see on top there is some Chinese writing. This gentleman was from East Asia and he had perfectly well controlled blood glucose levels most of the time, and you can see all these in marks which are put up there to show that he had these hypos going on. So something was amiss here. He was antibody negative. He improved dramatically with just mixed insulin. And his glucose control was fantastic now.

22:02 **Speaker:** Which changed him. Basically, what we did was we kept him under a close monitoring, we shifted him to sulphonylurea for a week's time and he maintained the same profile without any change. Now he's only on a DPP-4 inhibitor once a day. So from being managed on twice a day insulin, to managed just on a DPP-4 inhibitor, which was life changing for him. But it was also rewarding for us to say that we picked up somebody who probably had glucose toxicity related beta cell dysfunction or temporary seizure of its function, which recovered once we gave him some insulin and he was now back to his, what would beta cell functions there he's using it again now.

22:49 **Speaker:** So a similar presentation here was, this was the chap whom I remember very closely because he stopped taking insulin on his own accord, which I was not very pleased with, but he presented with polyuria, polydipsia, weight loss, typical symptoms of insulinopenia. He was from African origin you can see here. His HBA1c was 139 BMI again within normal range for Caucasian, but slightly high for a sub-Saharan person. So his antibodies where negative. He was managed on insulin initially, Humulin I 18 units.

23:27 **Speaker:** He was very reluctant to take his insulin and he stopped it once he was out of the hospital. But he maintained a very good HBA1c despite stopping insulin. So we persuaded him to at least use a small dose of DPP-4 inhibitor for postprandial hypoglycaemia if it occurs. And there are some studies to say that DPP-4 especially sitagliptin, was associated with some beta cell protection. So he's maintained on that. And he's just on the single dose of DPP-4 now.

24:02 **Speaker:** So why are these patients present differently and why where they Because we do know that there is an element called ketosis from diabetes, where some of the populations, especially South Asians, sub-Saharan and East Asian population, can have poor beta cell mass or the beta cell function could be stopped temporarily because of glucotoxicity. We have seen this in Caucasian population as well. And if we test them, if they're antibody negative or positive, it doesn't matter, but if they persist to have beta cell function because their glucose levels improves dramatically very quickly, they need very small amounts/dose of insulin per day, which are all tell-tale signs that there could be some beta cell function still left. So we can do some random c peptide levels on these patients. And if it is a good level we can continue on oral therapy for as long as possible and give them a break from the insulin. So it’s important, the reason why we need to get to the right diagnosis is so that we get to the right treatment as well.

25:19 **Speaker:** So the ketosis from diabetes, the most common variety where they’re antibody negative, but with some preserved beta cell function which we saw and there could be a variety of other things, they could be positive antibodies with some beta cell functions still left as well. But the most common one is where they are negative for antibodies but positive for c peptide levels.

25:41 **Speaker:** So moving on to another case, which is a 38 year old man, he was treated as possible LADA he was managed initially on metformin and DPP-4 inhibitor. And one fine day he suddenly deteriorated with regards to his glycaemic control and requiring insulin very quickly. So, again, a change antibody negative, but requiring insulin very quickly over a period of just a few months his glycaemic control worsened very quickly. So he was started on insulin and is now maintained well on insulin.

26:22 **Speaker:** So this is a gentleman who was antibody negative. But his beta cell function also failed very rapidly. So these are the idiopathic Type 1 patients, because sometimes we don't know why, because they’re antibody negative, unless they're positive, we don't brand them as Type 1s initially. But you can have an antibody negative Type 1 as well.

26:44 **Speaker:** So this is an interesting girl who presented to the GP surgery into acute admissions, so she was somebody who presented with recurrent UTIs and thrush. And despite the treatment, it didn't settle down and on one occasion the GP did pick up that her random blood glucose was 11.4. Previously when she went her glucose levels were found to be normal. She was sent into medical admissions unit querying whether this could be Type 1 because she had a normal BMI but no osmotic symptoms. Initial HBA1c was 44 mmols.

27:26 **Speaker:** So one of our endocrine SpR’s was on call, so he arranged to give her a glucose meter and got her into our medical clinic straightaway because she was not ketotic when she presented. So in clinic I spoke to her and she said that her mom is very well controlled diabetic, has diabetes, and she's only on metformin. And she also told me that her grandmother has Type 1 diabetes and she's one of the best control Type 1 diabetes patients because she's on minimal insulin with no complications and she can eat whatever she wants. That was one of the give-away things that there’s a good family history going on, somebody presenting in the second decade. And immediately we thought that this could be a more relax presentation.

28:10 **Speaker:** And this is her oral glucose tolerance test. You can see a set of fasting levels within normal limits. And at two hours, oral glucose tolerance test showed postprandial hypoglycaemia. So going back to my first slide which I showed you that she had, sorry I didn't put up the glucosuria picture here she wasn't. And when tested, she was positive for it and a 4Alfa mutation.

28:48 **Speaker:** So she is now managed, usually the treatment up until now was all to use gliclazide, we did use gliclazide initially, which caused tremendous hypos in her. She's managed on half a dose or 50 milligrams of sitagliptin now, and it's well controlled with no symptoms at all. And her younger sister, who's 11 years of age, has been tested as a casket screening and she was found to have the same mutation. So I suggested that her mom and grandmother can get checked as well, but they were not interested as they are well controlled on their treatment. She's gone from the local area. She's moved out now back to her place in England as she was studying here. So she's HNF4 alpha genetic diabetes, which is managed just on a DPP-4 inhibitor.

29:31 **Speaker:** So the diagnosis is quite important here to get to the right diagnosis. And we may not always get to the diagnosis in one go. That's one of the important key messages I would like to give today, is we can get it wrong in the first instance. But as long as we are treating the hypoglycaemia, not allowing for ketosis, then we are doing the right thing. But we should always keep the open mind to revisit it again, to say that the disease this is actually what the diagnosis we think of. So another case which might interest you is a 40 year old gentleman. He was diagnosed with Type 1 diabetes when he presented 20 years ago to hospital because he had very high blood glucose levels. Ketones were negative on that point. And because he was young, just 20, it was thought it was Type 1. And he has mild learning difficulties. His mom has looked after him all these years.

30:36 **Speaker:** Brilliant care. She has kept all the records of his blood glucose reading. So the gentleman is monitored by mum, and he was he was only on Humulin M3 20 units, twice a day. No hypos, no neuropathy, no retinopathy is again something we should think of, it could be excellent Type 1 control, but no hypos in all those years is something I cannot accept because we know that Type 1 diabetes and insulin management itself is a risk factor for hypoglycaemia. So we should always think, whether did we get the diagnosis right in the first time? And his antibodies were negative his C peptide when we did it randomly was in normal range.

31:23 **Speaker:** So after 20 years, this gentleman now for two or three years has stopped his insulin. Initially we managed him on gliclazide. He's lost a significant amount of weight, almost 20 kilograms since dropping insulin, he’s only on metformin monotherapy now. And the sad thing was the mom and son have not gone out of the country just purely because they were on insulin medications for all these years, because the risk of or a fear of hypoglycaemia.

31:54 **Speaker:** So the gentleman is fine. His control has not shifted from where it was, he’s holding between 48 to 56 mmols with a loss of 20 kilograms of weight and is doing well. He's really happy now that he doesn't need to check his glucose levels or take insulin. But it was an uphill task to bring him off insulin because he is used to the routine for such a long time. So again, questioning ourselves, whether we got the diagnosis right in the first instance, if it doesn't fit into all the aspects of clinical features, then there's no harm in revisiting the diagnosis.

32:33 **Speaker:** So the key pointers to consider would be how was it diagnosed? Was it symptom based, incidental blood test? How was the onset? Was it rapid, slow. BMI plays a huge role of course, phenotype, family history. Is any autoimmunity going on or any other autoimmune conditions, other associated features.

32:58 **Speaker:** So the reason we need to know all these things is we know that we have so many different treatment options nowadays. And we move away from a reduction to cardio protective versions of management with which comes a lot of new medications and risks of these medications, including ketoacidosis as well, especially with SGLT2 inhibitors so getting the right diagnosis so that we get the right treatment across, that's the reason.

33:32 **Speaker:** And as you know, even the latest guidance, which is probably going to change again now with NICE guidance in draft format now and it'll align with the ADA EASD guidelines. So if we get the right diagnosis, then we can go around looking for the right treatment as well, which will be hugely important in patient care.

I'm happy to take any questions from here.

33:55 **Chair:** Thank you Vinay. We haven't actually got any questions in the chat bar. You've stunned them with everything, the slide 38 have you got slide 38, the slide before that one. So as part of our planned webinars, there is new NICE guidance on managing Type 2 diabetes coming out early next year.

34:25 **Speaker:** Yeh it’s in draft format now.

34: 28 **Chair:** You've seen a draft of that. So we're going to be doing Diagnosis and then we're going to do the pre-diabetes and looking the lifestyle management and then looking at remission. And then hopefully by the time we get to early next year talking about management of Type 2 diabetes, the NICE guidance will be out and we can use that. The American Diabetes Association slide can you download that just from the website?

34:56 **Speaker:** Oh, it's available widely. One of the ADA 2021 guidelines for classification of diabetes or management of diabetes. It's a free PDF format which you can get. You can just Google it and standards of care ADA, if you Google it, you'll get it. So I just put across here ADA standards of care ADA 2021. You’ll get the latest ones usually and it's updated every year. So it's quite a handy few hundred pages, but you don't have to have all the things. But it's very easy to reference as well. And it's well written.

35:45 **Chair:** Thank you. Well, there aren't any other questions, which means everyone's happy with presentation or they don't have anything else to query. Oh we’ve got one coming now, the case of the young girl with the recurrent UTI and thrush. That's a very common presentation. What they're asking is, should we be doing routine blood sugars on all people with UTIs and thrush?

36:09 **Speaker:** Ah, that's quite difficult isn't it, because thrush is such a common condition. But if it's happening recurrently, you should check the blood glucose levels. I think that's a good start. Is there any other reasons. Recurring UTIs can also happen quite often, but thrush is something that we have to be aware that it's usually associated with hypoglycaemia. So if it's recurrent, yes, I would say.

36:44 **Chair:** In that case, in that particular case the HBA1c was normal

36:54 **Speaker:** Normal, yeah

36:54 **Chair:** If we used that we would have missed

36:54 **Speaker:** If you use HBA1c, but she's a 19 year old with prediabetes, with a normal BMI. Why should she have, so that will still be something we should consider. I think the clinical pointers to be aware of is the rapidity of onset phenotype and family history gives a lot of information and the story will just build upon that one.

37:18 **Chair:** Thank you very much. OK there's no further questions. Thank you very much Vinay it was a very clear and succinct presentation.

37:33 **Speaker:** Thank you.

37:33 **Chair:** Thank you all for our delegates for coming tonight. We know everyone's very busy and we'll look forward to seeing you in the next month or so talking about prediabetes and how to prevent people getting diabetes in the first place. Thank you very much. Thank you.