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The development of next generation screening and diagnostic platforms will change diabetes care

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Abstract

Diabetes mellitus is a common disease with a rising incidence and the findings of hyperglycemia and glucosuria. However, there are multiple types of diabetes, each with distinct etiologies. The two major types of diabetes are: type 1, which is caused by an autoimmune process, and type 2, which is thought to be primarily metabolic, resulting from insulin resistance, often in the setting of obesity. Historically the distinction between these two types was obvious. Here we discuss how this paradigm has dramatically changed both because of the evolving epidemiology of diabetes mellitus as well as new and emerging tools and therapies to diagnose and treat diabetes. As we believe that understanding these changes is critical to providing optimal care to patients with diabetes, we have developed a novel plasmonic gold chip platform that is able to meet the new and emerging demands of modern diabetes care.

Keywords

Diabetes; diabetes mellitus; plasmonic gold chip; autoantibodies

Introduction

Diabetes mellitus, a disease of hyperglycemia and metabolic derangement, results from a deficiency in insulin secretion and/or action. There are two major types of diabetes: type 1 (T1D), which is caused by an autoimmune process that is unrelated to the patient's weight, and type 2 (T2D), which is thought to be primarily metabolic, resulting from insulin resistance, often in the setting of obesity. However, there is nothing about one type of diabetes that is protective against the other type. Furthermore, in recent years, the incidences

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of both T1D and T2D have climbed dramatically [1,2]. These dynamic changes, coupled with new and emerging therapeutic options, have created a paradigm change in how we approach diagnosing diabetes.

The exact reason(s) for the rise in the rate of T1D remains elusive but has resulted in a significant increase in the number of adults that are now developing T1D [3,4]. On the other hand, the rapid rise in the rate of obesity has been broadly apparent throughout the globe since at least the early 1990s, raising alarms of impending medical complications; importantly, this has also impacted the pediatric population [2,5]. A rising incidence of childhood onset of T2D is at the forefront of this new reality with parts of the USA experiencing levels of T2D that have encompassed up to 50% of the pediatric diabetes cases [1]. Furthermore, obesity does not protect against the development of T1D [6]. Therefore, with the rise in obesity, T2D and T1D, the classic paradigm where T1D was a disease of thin children and T2D was a disease of obese adults is now obsolete and it is no longer possible to predict which type of diabetes a patient with new-onset disease has developed [4]. This has created a diagnostic dilemma as both T1D and T2D present with similar symptoms but can require very different treatment approaches [7]. Therefore, it is critical that objective diagnostic testing is rapidly performed as part of the initial evaluation of patients with new-onset diabetes.

Classification of Diabetes Mellitus

Type 1 Diabetes Mellitus

T1D is the consequence of autoimmune-mediated destruction of insulin-producing pancreatic beta-cells [8]. In other words, the patient's immune system mistakenly recognizes beta-cells as foreign invaders and launches an attack against them like they were an infection. The trigger for this inappropriate attack remains unidentified but the subsequent inflammatory response results in death of beta-cells that ultimately impairs the pancreas' ability to secrete insulin [3]. Hyperglycemia occurs when roughly 70–80% of beta-cells have become nonfunctional [4]. Some people with T1D will initially present with diabetic ketoacidosis (DKA) but the majority will present with symptomatic hyperglycemia without DKA as long as insulin therapy is started rapidly [8]. Importantly, a delay in the diagnosis of T1D and initiation of insulin therapy as short as 24-hours may result in a four-fold increased risk in progression to DKA – the number one cause of death with T1D [9].

In the recent past, T1D was considered a disease of early childhood and was termed "juvenile diabetes." More recently the incidence and prevalence have dramatically risen in both children and adults [4,5,10]. With the high prevalence of obesity, BMI is no longer a distinguishing characteristic [11,12]. While high-risk HLA gene variants are strongly linked to T1D, those affected have become the minority of patients over the past several decades [13–15]. In turn, family history of T1D is not a specific predictor of disease, and 85–90% of T1D patients do not have an affected relative [13]. As a result of these changes, physicians can no longer rely on epidemiologic markers to reliably classify the type of diabetes at presentation and this fact mandates the use of objective diagnostic testing. The detection of autoantibodies against one or more pancreatic islet antigen (insulin, glutamic acid decarboxylase (GAD65), tyrosine phosphatase islet antigen 2 (IA2 or ICA512) and/or zinc

transporter 8 (ZnT8)) is pathognomonic of T1D and therefore can be used to distinguish T1D from other forms of diabetes in a patient with hyperglycemia [7].

Type 2 Diabetes Mellitus

T2D is thought to result from pancreatic beta-cell stress related to an increased functional requirement secondary to a sedentary lifestyle, poor diet and persistently elevated insulin levels [8]. The hyperglycemia is commonly present for a long period of time before diabetes is diagnosed and this further compounds the beta-cell compromise [8]. This pattern results in a combination of insulin resistance and inadequate compensatory insulin secretion [6,8,10]. Importantly, the T1D diagnostic autoantibodies are not present in patients with T2D [6–8].

T2D is the most common form of diabetes worldwide. While seeming counterintuitive to some, there is actually a stronger genetic predisposition for T2D within families than with T1D [8]. Most children with T2D have some degree of obesity and, as the pediatric obesity rate continues to rise, so does the incidence and prevalence of pediatric T2D [5]. Currently, T2D accounts for up to 50% of new-onset diabetes presentations in American youth [1], and is projected to become the most common type of diabetes in adolescents in the next 10–20 years [16]. This dynamic pattern shift is occurring globally [2], and T2D already accounts for 80% of pediatric diabetes in Japan [16]. While obesity and insulin resistance in the USA disproportionately affect minority race/ethnic groups, no group is exempt from T2D or T1D [1].

As T2D is the most common cause of diabetes in adults, it is easy to assume a new-onset case in an adult is T2D. However, the practice of following these assumptions misses the patients that have T1D and current estimates indicate that 5–15% of adults with T1D are initially misdiagnosed as T2D with a resultant increased risk of complications from insulinopenia including DKA [4]. This number is increasing annually as the rate of T1D in adults increases. Conversely, children with T2D are often misdiagnosed as T1D [15]. In turn, these children with T2D are sometimes unnecessarily admitted to the hospital for intense multi-daily insulin injection education and treated with exogenous insulin with resultant increased risk of hypoglycemia and may exacerbate weight gain, hypertension and hyperlipidemia. Given that patients with new-onset T2D are less likely to require hospitalization, misclassification as T1D unnecessarily increases parental stress and healthcare expenditures.

Monogenic Diabetes

Monogenic onset diabetes of the young (MODY) manifests as hyperglycemia with an inappropriate insulin response due to an inherited monogenic mutation in a transcription factor [13]. Affected patients are frequently misdiagnosed as T1D when diagnostic testing is not performed. Patients with MODY will test negative for the T1D associated autoantibodies making this a valuable step in their work-up. Next generation sequencing has expedited the genetic confirmation of the MODY diagnosis in these patients that test negative for autoantibodies [17,18].

Diagnostic Criteria for Diabetes Mellitus

Fasting Plasma Glucose (FPG)

FPG ≥ 126 mg/dL following no caloric intake for at least 8 hours meets diagnostic criteria for diabetes [8]. In the absence of overt hyperglycemia, an abnormal FPG result should be repeated on a different day before the diagnosis is confirmed. Individuals with a FPG value of 100–125 mg/dL are thought to have impaired fasting glucose and are considered at-risk for progression to diabetes [8]. This test is unable to distinguish between T1D and T2D.

Random Plasma Glucose

Random plasma glucose ≥ 200 mg/dL in a patient with classic symptoms of hyperglycemia is diagnostic of diabetes mellitus but does not identify which type of diabetes [8]. In addition, a normal random glucose level does not rule-out diabetes.

Hemoglobin A1c (HbA1c)

HbA1c reflects the average blood sugar levels that were present in the body over the previous 3 months and does not require a fast. A reproduced HbA1c value of ≥6.5% is diagnostic of diabetes mellitus but does not identify which type of diabetes [8]. Other limitations of this test include non-interpretable values in patients with abnormal erythrocyte lifespan including hemoglobinopathies and iron deficiency anemia.

C-peptide

Measurement of c-peptide (a surrogate marker for insulin secretion) was once thought to distinguish T1D from T2D with a low value in the former and an elevated value in the latter. However, studies have shown that 4 out of 5 patients with T1D have normal c-peptide levels at the time of diagnosis [7,15,19]. Furthermore, patients with T2D frequently have low c-peptide levels at the time of acute presentation [6]. Therefore, c-peptide levels cannot be used to distinguish T1D from T2D.

T1D Specific Autoantibodies

Detection of T1D specific autoantibodies is the only laboratory test available that reliably distinguishes T1D from T2D and other types of diabetes [6,8,20]. The presence of an autoantibody (concentration above a defined positive threshold for the platform) against any one of the four pancreatic antigens confirms T1D in a patient with hyperglycemia [7,8,20]. However, currently antibody test results may take days to weeks to return, extending beyond the clinically important window for the physician to determine the optimal initial therapeutic approach [6]. The reason for this delay is related to dependence on the radioimmunoassay platform (RIA), which is slow, resource heavy and cannot be reliably performed in local laboratories [21,22]. Because of this important clinical need to definitively diagnose diabetes rapidly and close to the bedside, a large research effort by multiple groups has focused on the development of next generation diabetes diagnostic platforms capable of detecting T1D autoantibodies. We recently developed a plasmonic gold chip that is able to detect T1D specific antibodies in less than 2 hours using a fraction of the labor and resources required for RIA [22]. We believe this technology will enable physicians to rapidly complete the

diagnostic work-up that distinguishes T1D from T2D and, therefore, facilitate the initiation of patient specific care at the time of diagnosis.

Diabetes Autoantibodies

T1D specific autoantibodies not only confirm an autoimmune etiology in patients with new-onset diabetes, they are also validated predictive biomarkers of T1D in asymptomatic people [20,23]. The T1D autoantibodies can be present as early as infancy and many years before the onset of symptoms, making them highly useful in screening populations to predict who is likely to progress to develop diabetes [23,24]. In a study of first-degree relatives (before identification of the ZnT8 autoantibody), the five-year risk of developing T1D ranged from 0% in autoantibody negative individuals to 100% when all three known autoantibodies were detected [25]. A screening study of 4,505 otherwise healthy school children revealed that detecting at least two autoantibodies predicted who would develop T1D over an 8 year time period [26]. Together, these studies strongly underscore the importance of expanding screening programs for these highly informative markers. The cost and time of performing RIA prohibit the use of this platform for screening tests and, we believe, this is an additional critical area where the plasmonic chip will be deployed to meet the medical need.

The Future of Diabetes Care

Early identification of individuals at-risk for T1D is our best chance for diabetes prevention [3,27]. Emerging results from immunomodulation trials suggest that, in the future, a cocktail of interventions in at-risk individuals will limit beta cell destruction and preserve endogenous insulin production. Current results from these studies support that initiating such therapy as early as possible will improve efficacy. Again, technological limitations for autoantibody detection have been a barrier to the ability of physician to detect and intervene rapidly. With improved capability to readily detect T1D specific autoantibodies, therapeutic interventions may be implemented earlier in the natural history of the disease, potentially stopping progression to insulin dependence [3,4]. This is not only critically important in developed nations where rates of T1D continue to rise, but also in parts of the developing world where insulin dependence is synonymous with death in <1 year.

Conclusion

The rises of both T1D and T2D, as well as the evolving demographics of these diseases has changed the landscape of diabetes. Previous epidemiologic assumptions about which patient gets each type of diabetes are obsolete and can place patients at risk for misdiagnosis and a potentially dangerous delay in appropriate therapy that is individualized to their type of diabetes. As the rates of both types of diabetes continues to increase and the opportunities to modulate disease progression emerge, the problem of rapidly distinguishing these two diseases will become both more challenging and more important. Essential to addressing this problem is increasing the use of testing that definitely distinguishes T1D from T2D. We believe that the technological advance offered by the plasmonic gold chip could change the landscape of diabetes to enable early detection and rapid, patient specific treatment.

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Abbreviations

ADA	American Diabetes Association
DKA	diabetic ketoacidosis
MODY	monogenic onset diabetes of the young
FPG	fasting plasma glucose
HbA1c	hemoglobin A1c
OGTT	oral glucose tolerance test
T1D	type 1 diabetes mellitus
T2D	type 2 diabetes mellitus
WHO	World Health Organization

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