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Contents

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EDITORIAL

REVIEW

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Contents

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Xiu-Xia Song, Vice Director
World Journal of Diabetes
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
E-mail: editorialoffice@wjgnet.com
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EDITORIAL

Gestational diabetes mellitus: Screening with fasting plasma glucose

Mukesh M Agarwal

Mukesh M Agarwal, Department of Pathology, College of Medicine, UAE University, PO Box 17666, Al Ain, United Arab Emirates

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Correspondence to: Mukesh M Agarwal, MD, FCAP, Professor, Department of Pathology, College of Medicine, UAE University, Khalifa Bin Zayed Street, Tawam Hospital Campus, PO Box 17666, Al Ain, United Arab Emirates. magarwal7@gmail.com
Telephone: +971-3-7672000
Fax: +971-3-7671966

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Abstract

Fasting plasma glucose (FPG) as a screening test for gestational diabetes mellitus (GDM) has had a checkered history. During the last three decades, a few initial anecdotal reports have given way to the recent well-conducted studies. This review: (1) traces the history; (2) weighs the advantages and disadvantages; (3) addresses the significance in early pregnancy; (4) underscores the benefits after delivery; and (5) emphasizes the cost savings of using the FPG in the screening of GDM. It also highlights the utility of fasting capillary glucose and stresses the value of the FPG in circumventing the cumbersome oral glucose tolerance test. An understanding of all the caveats is crucial to be able to use the FPG for investigating glucose intolerance in pregnancy. Thus, all health professionals can use the patient-friendly FPG to simplify the onerous algorithms available for the screening and diagnosis of GDM - thereby helping each and every pregnant woman.

Key words: Gestational diabetes mellitus; Screening; Diagnosis; Fasting capillary glucose; Fasting plasma glucose

Core tip: The algorithms for the screening and diagnosis of gestational diabetes mellitus (GDM), advocated by various expert panels, are demanding for both the caregiver and the care-receiver: The widely accepted approach of screening all pregnant women with the oral glucose tolerance test is time-consuming, expensive and unfeasible in most countries. Over three decades of research, summarized in this review, suggests that the fasting plasma glucose can simplify the approach to GDM - only if all the limitations of using it are clearly understood.

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INTRODUCTION

For many years, gestational diabetes mellitus (GDM) was defined as hyperglycemia first discovered during pregnancy. However, due to the recent epidemic of type 2 diabetes mellitus afflicting numerous younger women in the child-bearing age, this traditional definition has been redefined. The World Health Organization (WHO)[1] classifies hyperglycemia first identified in pregnancy as: (1) diabetes mellitus in pregnancy; and (2) GDM. GDM generally refers to milder hyperglycemia and lesser degree of glucose intolerance occurring in the latter half of pregnancy, which usually does not persist after delivery in most patients. According to the American Diabetes Association (ADA), GDM is diabetes diagnosed in the second or third trimester of pregnancy that is not type 1 or type 2 diabetes mellitus (T1DM or T2DM)[2]. T1DM is caused by absolute insulin deficiency with positive autoimmune markers which destroy pancreatic β-cells, while T2DM is caused by insulin resistance or relative insulin deficiency. Clearly, GDM is distinct from both these types of diabetes[2]. The reason to segregate women with DM who become pregnant is because these women have more severe complications compared to pregnant women with GDM. However, GDM is also associated with many maternal (preeclampsia, increase in cesarean sections, birth injuries) and fetal problems (macrosomia, hypoglycemia, shoulder dystocia)[3]. After delivery, patients with GDM are at a risk of developing T2DM in the mother and childhood obesity in the neonate[4]. The pathogenesis of GDM is well-understood. The hormonal changes of pregnancy cause insulin resistance; most mothers compensate by increasing insulin secretion-something women with GDM are not able to do.

The diagnosis of GDM is confirmed by the 75 g or 100 g oral glucose tolerance test (OGTT). Screening for GDM can be done by: (1) clinical risk factors; (2) the glucose challenge test (GCT); or (3) the OGTT. Even though the ideal screening method is without consensus, screening generally involves a one-step or a two-step approach. In the one step approach, all patients undergo the diagnostic OGTT. In the two-step algorithm, screening is done either by: (1) assessing the clinical risk factors; or (2) the glucose GCT usually at 24-28 wk gestation, when venous plasma glucose is measured one hour after 50 g oral glucose. Patients who have clinical risk factors or exceed a specific GCT screening threshold undergo the diagnostic OGTT. However, due to an array of recommendations available (Table 1), the screening and diagnosis of GDM remains without consensus. Often, the obstetric and endocrine associations within the same country support markedly dissimilar protocols for GDM leading to major inconsistencies in the approach to GDM globally[5]. In 2010, the International Association of Diabetes and Pregnancy Study Groups (IADPSG) proposed a unified approach for screening and diagnosis of GDM advocating the 2 h, 75 g OGTT for all pregnant women at 24-28 wk[6]. Since its suggested glucose OGTT thresholds were based on the elaborate Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study[7], the IADPSG approach has been accepted by many reputed expert panels [*e.g.*, WHO, ADA and the Australasian Diabetes in Pregnancy Society (ADIPS)], but not all the major health organizations around the world [*e.g.*, the American College of Obstetricians and Gynecologists (ACOG) and the National Institute for Health and Care Excellence (NICE)].

Due to their wide acceptance, the IADPSG is best suited to be accepted world-wide. The International Federation of Gynecology and Obstetrics which has accepted the IADPSG criteria has issued a pragmatic guide for four categories: High, upper-middle, low-middle and low resource countries. Thus, depending on the resources, the IADPSG recommendations can be universally applied with modifications[8].

FEATURES OF A GOOD SCREENING TEST

The conventional thinking is that screening tests should be very sensitive (*i.e.*, without false negatives) so that no patient with the disease is missed, while diagnostic tests should be specific (*i.e.*, without false positives) so the diagnosis can be confirmed in all patients with potential disease (initially picked up by the sensitive screening test). In any population, a perfect screening test would separate all the patients with disease (defined by clinical criteria or a "gold-standard" test, *e.g.*, bone marrow stainable iron for iron deficiency anemia and OGTT for GDM) from all the healthy subjects. Thus, for GDM, the positive screening test should identify most women with GDM (true positives; the number of women picked up from all women with GDM will depend on the sensitivity) along with some women without GDM (false positives; the number of women falsely identified with GDM from amongst women without GDM will depend on the specificity), and the specific diagnostic test (OGTT in this case) will separate the true and false positives. However, usually due to overlap of the screening test results among the diseased and healthy population, choosing an appropriate cut-off (depending on the sensitivity/specificity combination desired) for the screening test would help it to become highly sensitive with minimum loss of specificity - something that may not be possible if there is a major overlap between the diseased and healthy populations. Thus, a screening test with poor specificity, *i.e.*, too many healthy testing as diseased (being over the threshold for diagnosis due to too many false positives) would have to proceed with the test needed to confirm the diagnosis. This would make the screening test of little use since its main function is to avoid the cumbersome and expensive diagnostic test. A screening test with 0% specificity, *i.e.*, when there is a total overlap of the diseased and healthy populations (Figure 1A), is useless. When there is less overlap between diseased and non-diseased, the performance of the screening test will be better (Figure 1B). The ideal state, when there is total segregation between diseased and healthy

Table 1 Diagnostic criteria for gestational diabetes mellitus (by country)

Organization	Use prevalent in	Year	Glucose load (g)	F mmol/L	1-h mmol/L	2-h mmol/L	3-h mmol/L	Values for diagnois
NDDG[1]	United States/North America	1979	100	5.8	10.6	9.2	8.1	⩾ 2
ADA (C and C)	United States/North America	2003 (1982)	100	5.3	10.0	8.6	7.8	⩾ 2
ADA[2]	United States/North America	2011	75	5.1	10.0	8.5	--	⩾ 1
CDA	Canada	2013	75	5.3	10.6	9.0	--	⩾ 1
EASD	Europe	1991	75	6.0	--	9.0	--	⩾ 1
NICE	United Kingdom	2015	75	5.6	--	7.8	--	⩾ 1
ADIPS[2]	Australasia	2014	75	5.1	10.0	8.5	--	⩾ 1
NZSSD	New Zealand	1998	75	5.5	--	9.0	--	⩾ 1
JDS[2]	Japan	2013	75	5.1	10.0	8.5	--	⩾ 1
IADPSG	Multiple countries	2010	75	5.1	10.0	8.5	--	⩾ 1
WHO[2]	Multiple countries	2013	75	5.1	10.0	8.5	--	⩾ 1

[1]Endorsed by American College of Obstetricians and Gynecologists; [2]Same as IADPSG. ADA: American Diabetes Association; ADIPS: Australasian Diabetes in Pregnancy Society; CDA: Canadian Diabetes Association; C and C: Carpenter-Coustan; EASD: European Association for the Study of Diabetes; JDS: Japan Diabetes Society; NDDG: National Diabetes Data Group; NICE: National Institute for Health and Care Excellence; NZSSD: New Zealand Society for the study of diabetes; WHO: World Health Organization; IADPSG: International Association of Diabetes and Pregnancy Study Groups.

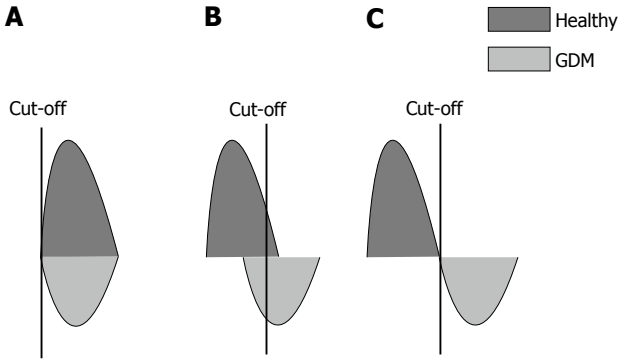

Figure 1 Effect healthy and diseased populations overlap on screening test performance (A-C). GDM: Gestational diabetes mellitus.

populations (Figure 1C), is a situation which is almost never achieved.

IS SCREENING FOR GDM WARRANTED?

In the past, there were extensive and acrimonious debates about the screening for GDM. Many questions have been raised: Should we screen pregnant women for GDM at all? Should screening be based on clinical risk factors only? Is screening with GCT a valid and potentially the best approach to screening? What is the most cost-effective way to screen for GDM? How good are other screening methods like fasting plasma glucose (FPG), glycated albumin and $HBA1_c$?

Screening for GDM does not meet many of the screening criteria set by the United Kingdom National Screening Committee, which is a modified version of the WHO criteria for assessing proposed screening programs[9]. Despite this, most preeminent professional societies, *e.g.*, ADA and WHO, recommend screening for GDM. In 2002, a thorough review by the Health Technology Program, United Kingdom[10] concluded, "On balance, the present evidence suggests that we should not have universal screening, but a highly selective policy, based on age and overweight (of patients)".

In 2008, after reviewing all the evidence, the preeminent United States Preventive Services Task Force (USPSTF) determined that the evidence was insufficient to assess the benefits and harms of screening for GDM. However, in 2014, the USPSTF (after another comprehensive follow-up review) advised that asymptomatic women after 24 wk of gestation should be screened for GDM, though before 24 wk, the evidence was insufficient[11].

If it is decided to screen for GDM, there is debate about the best way to screen for GDM. Though originally screening *via* risk-factors (age, obesity, family history of DM, GDM in previous pregnancy, non-white race, previous miscarriage/stillbirth/fetal malformation/preeclampsia/macrosomia) was widely recommended, many studies recommend otherwise: A recent comprehensive study found that this approach would miss a third of women with GDM[12]. In another recent commentary about the ideal way to screen, an editorial in a preeminent journal argued that whichever way one looks at it, there is no justification for either risk-factor or GCT based screening[13]. Their advice: The OGTT should be used for both screening and diagnosis of GDM-as recommended by the IADPSG. Though the cost of screening increases and more women are labelled as GDM, the St. Carlos study confirms that in the long term it is cheaper due to the fewer complications[14].

Many laboratory screening tests have been tried for screening of GDM. They are direct glucose measurements (FPG, GCT) or indirect measurements of glucose (HBA1c, fructosamine). Newer markers (insulin, irisin, galanin, adiponectin, sex hormone-binding globulin, C-reactive protein, fibrinectin, glycosylated fibrinactin, ferritin, glycated CD59) especially in early pregnancy have been tried to predict GDM later in pregnancy. However, only GCT and FPG have shown some promise. The holy grail of screening for GDM has yet to be found.

OGTT AS A GOLD STANDARD FOR DIAGNOSIS OF GDM AND DIAGNOSTIC CRITERIA

As pointed earlier, all the expert panels agree that the OGTT is the "gold standard" for GDM diagnosis. The OGTT has many drawbacks, the most serious flaw being that it is not reproducible[15]. It is expensive, time consuming and quite demanding for both the patient and the laboratory; furthermore, it is also not physiologic, quite unpleasant, uncorrected for body weight and its predictive value changes with ethnicity due to varying prevalence of GDM[16]. As a diagnostic test for DM in non-pregnant adults, many arguments have been made for keeping the OGTT[17] or avoiding it[15]. Due to the numerous problems of the OGTT, since 1997, the ADA favors the FPG with a lower threshold (7.0 mmol/L), rather than the OGTT for the diagnosis of DM in non-pregnant adults-even though this approach has its critics[18]. However, there has been no debate about the OGTT as a diagnostic test for GDM. Despite the potential of nausea and vomiting in pregnant women[19], the OGTT remains the cornerstone for diagnosis of GDM. Though many alternatives for screening of GDM have been explored, however, only the OGTT is currently acceptable as the diagnostic test.

Additional tests with OGTT may help to improve its performance. Measuring insulin with the 100 g OGTT may identify a subgroup of women who do not meet the ACOG criteria for GDM as they have only one abnormal glucose value. It has been found that women who have raised one hour serum glucose post oral glucose may need more intensive treatment[20]. The diagnosis of GDM using OGTT in pregnancy are further compounded by the variation in guidelines of the various preeminent expert panels for the glucose load used (75 g *vs* 100 g) and, as mentioned earlier, in varying diagnostic glucose thresholds suggested for diagnosis. Thus, a pregnant woman has the potential for undergoing the onerous OGTT three times: First one at booking, second one at between 24-28 wk, and the third one post-partum, six weeks after delivery.

FPG AS A SCREENING TEST

Over time, the definition of GDM, laboratory methods for glucose, and the screening and diagnostic criteria of GDM have evolved. Initially, in 1985, an anecdotal report[21] first used fasting blood glucose (along with glycosuria) for screening pregnant women. The interest in FPG surged when the expert committee of the ADA preferred using the FPG with lower thresholds rather than the OGTT for DM diagnosis in non-pregnant adults. In 1999, once the WHO approved this ADA approach, FPG became even more accepted and popular. Later, some studies while studying GDM screening, accidentally found that the FPG may have value[22]. The first comprehensive study on FPG as a screening test was conducted by Sacks *et al*[23]. In fact, Professor David Sacks due to his extensive initial and subsequent pioneering and iconic studies should be credited for putting FPG as a screening test for GDM on the world map.

FPG AS A SCREENING TEST: ADVANTAGES AND DISADVANTAGES

As a screening test for GDM, the FPG is very appealing: It cheap, reliable, reproducible, does not produce vomiting as seen with the OGTT/GCT. Thus, it can be administered in women unable to tolerate glucose drink and it takes less time than GCT. Using the FPG make GDM screening and diagnosis patient friendly[24]. However, the value of FPG for GDM screening remains uncertain. It is also not without problems. Incomplete fasting or an inability to fast for at least 8 h may not be easy for some pregnant women. In many poorer countries, multiple studies confirm that women find it hard to come to a clinic fasting. In some countries, fasting becomes hard if not impossible due to cultural beliefs that pregnant women should not fast for a long time, and commuting to the clinic takes an inordinately long time making it hard to fast. Often, the dropout rate is high when a pregnant woman is asked to come again for an OGTT after the clinic appointment. In some Asian populations, the FPG is inherently much lower (than Caucasians) but the postprandial is very high[25]. Thus, in India the authority on GDM, Diabetes in Pregnancy Study Group India advocates "a single-step procedure", *i.e.*, the 2-h glucose without fasting glucose for the screening and diagnosis of GDM[26].

THE PROBLEMS OF STUDIES EVALUATING THE FPG IN SCREENING

The potential problems in interpreting studies of screening with FPG are as follows: (1) numerous studies evaluating FPG screening have a pre-selection bias. Patients are selected on the basis of clinical history or positive GCT; then, they undergo an OGTT which is not done on all patients and compared to the FPG. This creates a higher prevalence of GDM, improving the predictive value of the FPG[27]. The entire population must undergo both the screening and diagnostic test. Any surrogate screening test should cannot be assessed using a biased population and applying findings to a healthy population[28]; (2) results in different populations have varying prevalence and cannot be compared. However, standardized procedures and ethnicity customization will improve reproducibility; (3) FPG performance is also difficult to compare between studies as differing criteria are used for the diagnosis of GDM; (4) studies should use FPG independent of the OGTT to evaluate its performance. Using the FPG of the OGTT is erroneous as it assumes FPG is reproducible, which may not be so; and (5) in most reports, FPG performance is compared to the OGTT rather than examining how the test predicts

Table 2 Studies about fasting plasma glucose as a screening test

n	Cut-off mmol/L	Se (%)	Sp (%)	GDM (%)	AUC	Glucose load (g)	OG criteria[1]	Ref.
Without selection bias								
5010	4.5	81.5	54	7.6	--	75	WHO-1985	Reichelt *et al*[37]
558	4.8	81	76	10.2	0.897	100	ADA	Perucchini *et al*[27]
942	4.1	> 70		13	0.766	75	WHO-1985	Tam *et al*[38]
1685	4.7	78.1	32.2	19.8	0.639	75	WHO-1999	Agarwal *et al*[39]
500	4.7	88	95	7.2	--	100	C and C-1982	Poomalar *et al*[41]
In early pregnancy								
4507	4.6	80	43	6.7	0.7	75	Sacks	Sacks *et al*[46]
708	4.7	79.9	27.5	25.9	0.579	75	WHO-1999	Agarwal *et al*[47]
4876	4.4	79	46.9	2.8	0.72	100	C and C 100-g OGTT	Riskin-Mashiah *et al*[49]
17186	4.3	84	29	12.4	--	75	IADPSG	Zhu *et al*[51]
486	--	47.2	77.4	10.9	0.623	--	FPG > 5.1 mmol/L	Yeral *et al*[53]

Fasting plasma glucose (FPG) threshold with Specificity (Sp) corresponding to Sensitivity (Se) about 80%. AUC: Area under receiver operating characteristic curve; C and C: Carpenter-Coustan; ADA: American Diabetes Association; WHO: World Health Organization; IADPSG: International Association of Diabetes and Pregnancy Study Groups; OGTT: Oral glucose tolerance test; GDM: Gestational diabetes mellitus.

poor health outcome. It has been suggested that the "gold-standard" for screening tests would be a universally agreed-on set of pregnancy outcomes[29].

BIASED REPORTS ON GDM SCREENING WITH FPG

As pointed earlier, to evaluate any screening test, the screening test and the diagnostic test must be done in the entire cohort. Otherwise, the evaluation is not accurate. In FPG screening, this is often not the case since only the positive screen patients (by clinical risk-factors or the 50-g GCT) undergo the OGTT. The FPG performance is compared to these fewer preselected patients who undergo the OGTT. These earlier studies by Sacks *et al*[23], de Aguiar *et al*[30], Agarwal *et al*[31,32], Rey *et al*[33], Soheilykhah *et al*[34], Senanayake *et al*[35] and Juutinen *et al*[36] suffer from this drawback (Table 2).

UNBIASED STUDIES ON FPG SCREENING FOR GDM

In 1998, the first comprehensive unbiased study of FPG screening for GDM was from Brazil (Table 2). Based on this study, Brazil became one of the few countries that recommend using FPG as a screening test for GDM in their national guidelines. Reichelt *et al*[37] analyzed the value of FPG as a screening test for GDM in 5010 women. The FPG performed well in the 16 (0.3%) women with frank diabetes (2-h > 11.1 mmol/L). However, in most of the other 363 (7.2%) women with reduced and compromised glucose tolerance (GIGT, 2-h = 7.8-11.0 mmol/L), despite the author's claim, the performance was less than satisfactory. At their ideal cut-off of 4.7 mmol/L, both the sensitivity and specificity for women with GIGT were too low to be of any use (68.0%). If the threshold was decreased to 4.5% mmol/L, the sensitivity and specificity would be 81.5% and 54%; 51% women were less than this threshold. Thus, approximately one in two of their pregnant patients would have to proceed to the diagnostic OGTT to pick up 8 of 10 women with GDM. The increased number of false positives would make FPG as an inefficient screening test for GDM.

The 1999 study by Perucchini *et al*[27] evoked a lot of interest in FPG since it was published in the preeminent British Medical Journal. In 520 women who were pregnant the FPG performed better than the OGCT (Carpenter and Coustan criteria, C and C, using the 3-h, 100 g OGTT). FPG as a screening test had a good overall sensitivity and specificity. However, the number of women was small and the cohort was very small.

In 2000, Tam *et al*[38] from Hong Kong, inspired by the Reichelt study, compared 50 g glucose challenge, FPG, random glucose and fructosamine in 942 women who were pregnant. The prevalence of GDM (1980 WHO criteria) was 13%; since the area under a receiver operating characteristic curve (AUC) for GCT, FPG and 2-h glucose were similar, due to its simplicity, they recommended universal screening using FPG (cut-off 4.1 mmol/L) rather than the GCT.

In 2005, in one study involving 1685 pregnant women (WHO GDM criteria for the 75 g OGTT)[39], we found that the elevated number of women testing as false-positive made the FPG an inefficient test for GDM screening. Subsequently, a year later, we showed that[40] the variation in FPG performance may be due to the differing diagnostic criteria used for the diagnosis of GDM. The performance of FPG as a screening test with 4 different diagnostic criteria (using the same 75 g OGTT) was compared. In 4602 women, the FPG efficiency as a screening test was a function of the criteria used for diagnosis; it was excellent when the ADA-2003 criteria were used for diagnosis. With the other three criteria (WHO, ADIPS, European Association of Study on diabetes), at a satisfactory 85% sensitivity, the increased FPR and low specificity limited the value of FPG in screening.

More recently in 2013, Poomalar *et al*[41] compared FPG and GCT as screening tests. They found (like Peruchini's study) that the ROC curve for FPG was better

than GCT. However, their numbers were also small (500 women) and one is uncertain about the randomization of their subjects and the number of women missed during the study period.

FPG AS A SCREENING TEST FOR GDM IN EARLY PREGNANCY

In screening for GDM in early pregnancy (Table 2), two questions arise: (1) can the diagnosis of GDM be made in early pregnancy? and (2) how to interpret a raised FPG in early pregnancy.

In 2014, as stated earlier, the USPSTF concluded that the evidence was not enough to assess the balance of benefits and harms of screening for GDM in asymptomatic pregnant women before 24 wk of pregnancy[11]. It has been shown that higher first trimester FPG levels increase the risk of adverse pregnancy outcomes[42]. Some experts have cogently argued that the IADPSG recommendation (endorsed by WHO) that an FPG of 5.1-6.9 mmol/L be classified as GDM in pregnancy cannot be accepted as there are no controlled trials that address the benefits of diagnosing and treating GDM in early pregnancy[43]. Even the ADA does not support the IADPSG view to diagnose GDM in early pregnancy.

Physiologically, in non-obese women, there is a fall in FPG in early pregnancy (median 0.11 mmol/L between 6-10 wk gestation), thereafter the glucose levels decrease little. Eight of ten studies showed a decrease in the first trimester[44]. A more recent study observed the same finding about FPG, while in the second to the third trimester, most studies have shown that the FPG changed little[45]. Thus, the thresholds used in third trimester for GDM diagnosis-on a theoretical basis-cannot be used in the first trimester.

The controversies about GDM diagnosis in early pregnancy notwithstanding, different studies have addressed this issue about FPG screening in early pregnancy with mixed results. Sacks *et al*[46] concluded that in their 5557 women during the first prenatal visit, despite good compliance, the poor specificity of FPG made it an inefficient test for screening for GDM. Similar conclusions were drawn by us[47] in a highrisk population. However, Corrado *et al*[48] observed that a FPG $\geqslant$ 5.1 mmol/L predicts GDM in later pregnancy. Similarly, Riskin-Mashiah *et al*[49] found that FPG may be used as a screening test to assess risk, but not as a diagnostic test in early pregnancy: A higher FPG in the first trimester, even though in the normal range, constituted a risk for GDM in later pregnancy. Alunni *et al*[50], found that implementing FPG (and $HBA1_c$) screening in early pregnancy, nearly doubled the incidence of GDM and predicted the need for more pharmacotherapy. An extensive study by Zhu *et al*[51], involving 17186 women from China, showed that the first prenatal visit FPG correlated strongly with GDM at 24-28 wk gestation; however, they also assert that FPG $\geqslant$ 5.1 mmol/L should not be used to make a diagnosis of GDM in early pregnancy. They found that besides gestational age, chronological age also affects the FPG level as an independent variable. A study in 2004, on 246 women, found that FPG does not predict GDM in later pregnancy[52].

In 2014, Yeral *et al*[53] measured the FPG of 736 women during early pregnancy (1st visit) and randomized them (at 2nd visit) into: (1) the two-step 50 g GCT followed by 3-h, 100 g OGTT for positive results; and (2) the one step 2-h, 75 g OGTT repeating the tests in late pregnancy for women testing negative. GDM was diagnosed by Carpenter and Coustan criteria for 100 g OGTT and IADPSG criteria for the 75 g OGTT (in both second visit and late pregnancy). Within each cohort, the sensitivity in early pregnancy of 50 g GCT and 75 g OGTT was 68.2% and 87.1%, respectively. However, they reported the consolidated performance of FPG in early pregnancy (sensitivity 47.2%) for GDM diagnosed by the different criteria in the two groups. Since FPG performance is a function of the diagnostic criteria[40], individual performance of FPG is needed in each group to interpret their results further. Furthermore, the FPG results cannot be compared to other studies as two OGTT gold-standards were used.

In summary, most studies agree that the FPG in early pregnancy can predict risk for GDM in late pregnancy and possibly the need for medical therapy (and insulin). However, its poor specificity makes it an inappropriate test for screening test in early pregnancy - if and once the experts agree that GDM can be diagnosed in early pregnancy at all.

FASTING CAPILLARY GLUCOSE AS A SCREENING TEST FOR GDM

Few studies have addressed the value of fasting capillary glucose (FCG) as a screening test for GDM. There is an excellent correlation between fasting capillary glucose and fasting venous fasting glucose in pregnant women[54]; thus, the fasting capillary glucose shares the same performance characteristics as the fasting venous glucose.

Three studies have reported on the value of FCG as a screening test for GDM. These studies were done in populations of countries at low risk (Sweden)[55], moderate risk (Canada)[56] and highrisk (United Arab Emirates)[57] for GDM. Both studies in the high risk population and lowrisk population showed a similar AUC (87%), sensitivity (86%), specificity (55%) at FCG thresholds of 4.0 mmol/L and 4.7 mmol/L, respectively. The study from Canada was designed differently; it used FCG in preselected patients who tested positive with 50 g GCT with the specific aim to define a threshold which could rule of GDM without the need for an OGTT. The AUC was modest at 0.67. The fasting capillary glucose was positively associated with OGTT glucose values, and inversely associated with insulin sensitivity and pancreatic beta cell function. However, due to the overlap of FCG in the GDM and non-GDM populations, it could not be used to rule out GDM reliably. All three studies show that, like

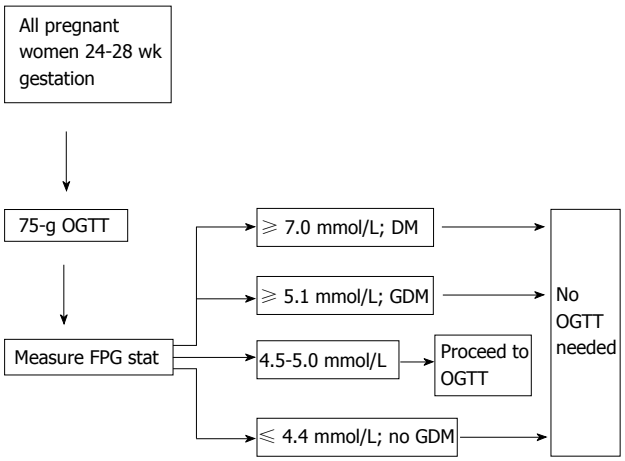

Figure 2 Suggested algorithm for gestational diabetes mellitus screening. OGTT: Oral glucose tolerance test; FPG: Fasting plasma glucose; GDM: Gestational diabetes mellitus; DM: Diabetes mellitus.

the FPG, the poor specificity precludes using FCG for GDM screening[58] since too many healthy women testing positive (false positives) would need the diagnostic OGTT. However, using the FCG (like FPG) may be of value to avoid a number of OGTTs needed, as discussed in the next section.

USING THE FPG TO DECREASE THE NUMBER OF OGTTS

The two-threshold method: Screening every pregnant woman for GDM with the OGTT, as advised by all expert panels (WHO, ADA, ACOG, CDA), is very demanding for the patient, the laboratory and the health-delivery system. Hence, there is a need for simpler, alternative screening tests. Screening tests are sensitive or specific, and generally, as the sensitivity increases, the specificity decreases and vice versa. So, to get the best of a screening test's performance, Henderson, a chemical pathologist, advocates using two-thresholds[59]. In short, two threshold values, instead of one cut-off (as is the common practice), are utilized for the screening (*e.g.*, fasting glucose for GDM). The higher cut-off, the specificity of which is innately increased, is used to "rule-in" the disease (GDM here); while the lower cut-off with its inherently increased sensitivity is used to "rule-out" the disease. Subjects with results in between these two selected cut-offs, are "indefinite" and would need the diagnostic test. All subjects above the higher threshold and below the lower threshold, do not need to be evaluated further. Thus, the FPG can be used to limit the number of OGTTs in any population. The author of this review is a chemical pathologist; thus, being aware of the literature in clinical chemistry has been applying this method to GDM.

Thus, since 2000, in our UAE population, we have used the two threshold "rule-in and rule-out" algorithm GDM in multiple studies[32,39,40,60,61] (Table 3). Depending on the FPG result, the OGTT can be avoided completely: (1) the upper chosen FPG cut-off, "rules-in" GDM with 100% specificity, and (2) the lesser FPG cut-off selected "rules-out" GDM with variable sensitivity. Table 3 shows that between 25%-70% women would not need the OGTT using this algorithm. Studies from China[62] and Brazil[63] have shown similar results.

Therefore, using this approach, the FPG could tentatively avoid 33.0%-50.0% OGTTs, depending on the GDM diagnostic criteria[40,61]. Most countries still using the GCT for screening and OGTT for diagnosis may find it more cost-effective and simpler to switch to the OGTT for screening and diagnosis using the FPG decreasing the number of OGTTs needed-only after making sure this FPG-OGTT algorithm works in their population.

Rationale of using the 5.1 mmol/L and 4.4 mmol/L FPG thresholds: As per the criteria of the IADPSG, an FPG $\geqslant$ 5.1 mmol/L (independent of the other two values of the 75 g OGTT) confirms GDM. The lower cut-off of 4.4 mmol/L is derived from the elaborate HAPO study[7] which found that pregnancy outcomes were good when the FPG was $\leqslant$ 4.4 mmol/L. This approach is shown diagrammatically in Figure 2.

Shortcomings of the 2 threshold approach: There is a major difference in fasting glucose levels between 15 different centers distributed globally as shown by the HAPO study[64]. In some Asian populations, the FPG is very low but the postprandial is very high[25]. Thus, the suggested approach may, in many populations, may not circumvent too many OGTTs.

Another concern with approach is laboratory turnaround time (time taken to get the FPG result). If too long, this algorithm cannot be used. To decrease the turnaround time, a glucometer has been used to measure the fasting capillary glucose. The glucometer FCG has been found to be as good as the laboratory FPG with the excellent diagnostic correlation (κ = 0.95) for GDM[57].

COST OF SCREENING WITH FPG

Few studies analyzing cost of FPG screening compared to other screening methods are available. One study compared eight screening strategies[65]. It found that when the risk of GDM in a population was between 1.0%-4.2%, FPG followed by the OGTT was the cost-effective method. When risk was less (or more), other strategies were better. They also comment on another very important aspect of screening: Acceptance rates. The percentage of women who would undergo the screening test was as follows: OGTT, 40%; FPG, 50%; GCT, 70%; and RPG, 90%.

Another study[66], calculated the costs of three strategies: The 2-step (GCT + 100 g OGTT), the 1-step (75 g OGTT) and FPG of the OGTT to limit the number of OGTTs. Of the three strategies, the last one was the ideal approach.

FPG AS A POST-PARTUM SCREENING TEST AFTER DELIVERY

Since GDM is a marker for diabetes mellitus after delivery,

Table 3 Studies using fasting glucose to avoid oral glucose tolerance test

OGTTs circumvented (*n*, %)	Thresholds (lower and higher) mmol/L	OGTT (g)	Diagnostic criteria	Comments	Ref.
50.9	4.4 and 5.3	100	ADA (C and C)	Biased sampling: Preselected by clinical/GCT	Agarwal *et al*[32]
30.1	4.7 and --	75	WHO-1999	Only lower threshold used to rule out GDM	Agarwal *et al*[39]
63.8	4.9 and 7.0	75	ADA (C and C)	FPG screening dependent on GDM criteria	Agarwal *et al*[40]
68.5	4.9 and 7.0	75	ADA (C and C)	Glucometer used for FPG	Agarwal *et al*[60]
50.1	4.7 and 7.0	75	ADA (C and C)	Fasting capillary glucose used	Agarwal *et al*[57]
50.6	4.4 and 5.1	75	IADPSG	Pooled data from 4 studies	Agarwal *et al*[61]
50.3	4.4 and 5.1	75	IADPSG	Data from China corroborating UAE data	Zhu *et al*[62]
61.0	4.4 and 5.1	75	IADPSG	Data from Brazil corroborating UAE data	Trujillo *et al*[63]
57.0	4.4 and 5.1	75	IADPSG	Thresholds applied to HAPO Study	Agarwal *et al*[77]

OGTT: Oral glucose tolerance test; ADA: American Diabetes Association; WHO: World Health Organization; IADPSG: International Association of Diabetes and Pregnancy Study Groups; C and C: Carpenter-Coustan; GCT: Glucose challenge test; GDM: Gestational diabetes mellitus; FPG: Fasting plasma glucose; UAE: United Arab Emirates; HAPO: Hyperglycemia and Adverse Pregnancy Outcome.

it is obligatory to find the state of glucose tolerance in the immediate postnatal period and after long-term follow-up. All major guidelines recommend testing the mother 6-12 wk after birth of the baby; however there is a variation in the recommendations of the tests to use: FPG or the OGTT. The ADA and CDA recommend the OGTT, the NICE advocates FPG while the WHO and ACOG maintain that either test is acceptable[67]. The OGTT is more sensitive and picks up a higher number of women with dysglycemia, but the compliance is less (between 30%-70%). A ten year study showed that fasting glucose missed up 10% of women with DM and 60% women with impaired glucose tolerance[68]. We have reported that both tests show similar estimates for DM but widely discordant rates for glucose intolerance depending on the criteria used for DM diagnosis[69]. Kim *et al*[67] cogently argue that the decision could be based on the criteria used to pick up GDM antepartum. Thus, if the less stringent criteria are used (*e.g.*, IADPSG) which picks up more women with dysglycemia post-partum, it may be better to use the FPG since the disparity between the two will decrease when women with lesser degrees of glucose intolerance are identified antepartum[69].

OTHER STUDIES ABOUT FPG AND GDM

Atilano *et al*[22] found that an abnormal FPG $\geqslant$ 5.8 mmol/L predicted GDM much better than an abnormal GCT. In this study, very high FPG values showed an excellent positive predictive value (96%), but the corresponding sensitivity at these high levels would remain poor. However, their patient population was pre-selected by an abnormal GCT giving a high prevalence of GDM of 22% and there are many doubts if the conclusions can be universally applied. Herrera *et al*[70] in 324 patients with GDM (75 g OGTT at 24-28 wk by C and C criteria) found 7.0% women who had isolated elevated FPG were more likely to need hypoglycemic agents, have higher body mass index and be Black or Hispanic. Another study compared FPG and hs-CRP in the first trimester and found the former was more sensitive and the latter more specific[71]. A higher maternal fasting glucose during 4-12 gestational weeks in 57454 women was associated with an increased birth weight and birth length of the offspring during 6-12 mo of the infant's life[72].

STUDIES CHALLENGING THE USE OF FPG FOR GDM SCREENING

Many studies have found the FPG to be an inadequate test for GDM. Most of these studies are from South Asia, where women have lower FPG than their Caucasian counterparts. Balaji *et al*[73] found that FPG was inadequate as a screening test in their 1643 subjects from South India when compared to the WHO-1999 criteria. A threshold of 5.1 mmol/L had a sensitivity of just 24.0%. In another study[36] on 435 Finnish women with GDM (by the older criteria of the fourth International Conference-Workshop on GDM, a FPG threshold of 4.8 mmol/L picked up just 69.6% of the women with GDM). However, despite the poor sensitivity, FPG predicted the need for insulin. A 2003 study from Japan[74], found that in 749 Japanese women, a FPG threshold of 85.0 mg/dL had a sensitivity of 71.4% and 75.0 in first and second trimester, respectively; however, there were just 22 (2.9%) women with GDM (Japan Diabetes Association criteria).

FPG AND THE ROLE OF THE LABORATORY

FPG as a screening test for GDM: Other reviews

All reviews analyzing FPG as a screening test comment about the problem of analyzing the results. There is a lot of inconsistency and wide variation in the sensitivity and specificity found by these studies because of the ethnicity of the population, local prevalence and the diagnostic criteria used. In November 2012, the Agency for Healthcare Research and Quality of the United States Department of Health and Human Services[3], Maryland analyzed 7 studies on FPG to screen for GDM. They were unable to make any definite conclusions about the FPG as a screening test. They found that the FPG was not good at predicting an abnormal OGTT. In

2010, Virally *et al*[75] looked at 8 reports commenting on screening for GDM using FPG. Their conclusion was that due to the heterogeneity the studies were impossible to compare; some were in highrisk populations and the diagnostic criteria were very variable. They were critical of the fact that none of the GDM studies related to perinatal outcomes. In 2013, the USPSTF published a systemic review of screening tests for GDM[29]. At a FPG threshold of 4.7 mmol/L, the sensitivity was similar to GCT. However, the positive likelihood ratio (LR) of 1.8 compared unfavorably to the positive LR of 5.9 of the GCT. Thus, they concluded that FPG and GCT were good at identifying women who do not have GDM but the FPG was not as good as GCT to identify women who have GDM. They also found that FPG did not diagnose GDM as frequently in Asian as non-Asian women.

CONCLUSION

In general, for the screening of GDM, the FPG is more sensitive than specific, *i.e.*, it is better at "ruling-out" than "ruling-in" GDM[76]. Its performance is highly dependent upon the ethnicity of the population, the GDM prevalence, the diagnostic criteria and the FPG thresholds used. If these screening thresholds are kept low, the FPG will identify most women with GDM, but also an excessive number of women without GDM (due to poor specificity). Therefore, at an acceptable sensitivity, the poor specificity and high-false positive rate limit its usefulness as a screening test. However, as shown by studies originally from UAE, and reproduced by studies from China and similar studies from Brazil, it can still be very useful to decide if the OGTT is needed for diagnosis. Then, the FPG can help to reduce the number of onerous OGTTs required by nearly half[61,77]; however, 5%-15% patients with GDM would be missed, potentially women with lesser degrees of glucose intolerance - so health care will not be compromised. In summary, once its caveats are clearly understood, the FPG can simplify the screening and diagnosis of GDM. Thus, by circumventing the OGTT, the FPG can relieve many pregnant woman in the demanding work-up of glucose intolerance.

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REVIEW

Early detection of diabetic kidney disease: Present limitations and future perspectives

Chih-Hung Lin, Yi-Cheng Chang, Lee-Ming Chuang

Chih-Hung Lin, Yi-Cheng Chang, Lee-Ming Chuang, Department of Internal Medicine, National Taiwan University Hospital, Taipei 100, Taiwan

Chih-Hung Lin, Lee-Ming Chuang, Graduate Institute of Clinical Medicine, College of Medicine, National Taiwan University, Taipei 100, Taiwan

Yi-Cheng Chang, Graduate Institute of Medical Genomics and Proteomics, College of Medicine, National Taiwan University, Taipei 100, Taiwan

Yi-Cheng Chang, Institute of Biomedical Science, Academia Sinica, Taipei 115, Taiwan

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Correspondence to: Dr. Lee-Ming Chuang, MD, PhD, Department of Internal Medicine, National Taiwan University Hospital, 7, Chung Shan S. Rd, Taipei 100, Taiwan. leeming@ntu.edu.tw
Telephone: +886-2-23123456
Fax: +886-2-23938859

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Abstract

Diabetic kidney disease (DKD) is one of the most common diabetic complications, as well as the leading cause of chronic kidney disease and end-stage renal disease around the world. To prevent the dreadful consequence, development of new assays for diagnostic of DKD has always been the priority in the research field of diabetic complications. At present, urinary albumin-to-creatinine ratio and estimated glomerular filtration rate (eGFR) are the standard methods for assessing glomerular damage and renal function changes in clinical practice. However, due to diverse tissue involvement in different individuals, the so-called "non-albuminuric renal impairment" is not uncommon, especially in patients with type 2 diabetes. On the other hand, the precision of creatinine-based GFR estimates is limited in hyperfiltration status. These facts make albuminuria and eGFR less reliable indicators for early-stage DKD. In recent years, considerable progress has been made in the understanding of the pathogenesis of DKD, along with the elucidation of its genetic profiles and phenotypic expression of different molecules. With the help of ever-evolving technologies, it has gradually become plausible to apply the thriving information in clinical practice. The strength and weakness of several novel biomarkers, genomic, proteomic and metabolomic signatures in assisting the early diagnosis of DKD will be discussed in this article.

Key words: Diabetic kidney disease; Early diagnosis; Genomics; Biomarkers

Core tip: Estimated glomerular filtration rate (eGFR) and albuminuria are currently the standard method for

detecting diabetic kidney disease (DKD). Creatinine-based GFR estimates are affected by muscle mass and diet pattern, as well as the formula chosen. Albuminuria majorly reflects glomerular dysfunction, and is less sensitive to tubulointerstitial and vascular damages. These facts limit the application of eGFR and albuminuria in the early diagnosis of DKD, especially in heterogeneous type 2 diabetic patients. Through the assistance of genetic information for screening of susceptible patients, together with novel biomarkers to reflect diverse renal tissue damage, early diagnosis of DKD could be facilitated.

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INTRODUCTION

Diabetes mellitus is currently one of the most rapidly-growing "epidemics" around the world. According to the International Diabetes Federation, 415 million people are currently affected by this disease worldwide[1]. By the year 2040, the patient number is expected to rise up to 642 million, reaching a global prevalence of 10%[1]. This increasing number of patients, mostly with type 2 diabetes mellitus (T2DM), has influenced the rate of diabetic complications, including diabetic kidney disease (DKD). In developed countries, DKD is one of the most common complications of both type 1 diabetes mellitus (T1DM) and T2DM[2], and is also the leading cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD)[3-5]. The costs of care for patients with DKD are extremely high, especially after they enter ESRD. In the United States, for the patients covered by Medicare, the average cost per person per year was USD 20000, whereas it was USD 40000 in the younger group (below 65 years of age)[2]. This leads to an increasing burden on the finance and health care systems. Therefore, different methods for identification and management of patients with DKD, especially in the early stages, have always been the priority in the research field of diabetic complications. At present, diagnosis of DKD in clinical settings relies upon the assessment of kidney function, usually by calculating estimated glomerular filtration rate (eGFR), and the assessment of kidney damage, usually by checking urinary albumin-to-creatinine ratio [UACR, urine albumin (mg/L)/urine creatinine (mmol/L)] in random spot urine samples[6]. Although these tests can be performed easily, they have certain limitations. Therefore, understanding these limitations is important to both clinical applications and the future quest for better diagnostic methods.

NATURAL HISTORY OF DKD

The first clinical sign suggestive of DKD is glomerular hyperfiltration, which is observed in about 70% and 50% of the patients with T1DM and T2DM, respectively[7]. Due to the increased intraglomerular pressure, the elevation in GFR may exceed 120 mL/min per 1.73 m^2[8]. In some patients, hyperfiltration is followed by the development of albuminuria. Most patients with T1DM have a normal UACR (< 3.4 mg/mmol) during the first 5 years after the disease onset. In the subsequent 10-15 years, albuminuria develops in some patients, and progresses gradually if no intervention is taken. Once UACR is over 34 mg/mmol, the GFR decreases progressively at a variable rate. Approximately 50% of the patients with UACR > 34 mg/mmol progress to ESRD over a period of 10 years and approximately 75% of the patients over a period of 20 years[6]. In patients with T2DM, however, the natural course of DKD is less understood, as the diagnosis is usually delayed by many years. Some patients already display various degrees of albuminuria at the time of diagnosis; however, only 20% of the patients with UACR > 34 mg/mmol progress to ESRD over a period of 20 years[9,10].

LIMITATIONS OF EGFR

In terms of renal excretory functions, GFR is considered the best overall index. However, due to its time-consuming nature, the measurement of 24-h creatinine clearance to assess GFR is not always easily performed in clinical settings. Instead, to assess renal function, calculating eGFR using serum creatinine level and formulae such as the modification of diet in renal disease [MDRD, eGFR = 175 × standardized $Scr^{-1.154}$ × $age^{-0.203}$ × 1.212 (if black) × 0.742 (if female), where Scr is serum creatinine][11] or the chronic kidney disease epidemiology collaboration [CKD-EPI, eGFR = 141 × min (Scr/k, 1)$^{\alpha}$ × max (Scr/k, 1)$^{-1.209}$ × 0.993^{Age} × 1.018 (if female) × 1.159 (if black), where k is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/k or 1, and max indicates the maximum of Scr/k or 1][12] equations has become a routine practice. The National Kidney Foundation uses eGFR to classify stages of CKD[13]. Nonetheless, there are some potential flaws in using eGFR as a marker for the early diagnosis of DKD. First, serum creatinine levels are affected by the muscle mass and diet pattern (especially meat intake)[14,15], and therefore may interfere with the eGFR calculation. Second, the formula used may also cause imprecision in certain conditions. The MDRD equations become less reliable in patients with GFR > 60 mL/min per 1.73 m^2[16,17]. This would cause a considerable problem in the early diagnosis of DKD, as glomerular hyperfiltration appears early in the course of the disease. The CKD-EPI equation, on the other hand, is more accurate in patients whose GFR is > 90 mL/min per 1.73 m^2[18] and is, therefore, preferred when applying

it in patients with diabetes[6]. However, Camargo *et al*[19] reported a marked underestimation of GFR calculated with the CKD-EPI equation in diabetic patients compared to healthy individuals. Moreover, the MDRD and CKD-EPI equations have a P30 value between 80% and 90%, which means that the eGFR generated from these equations has, at best, a 90% chance of being within ± 30% of the measured GFR[2]. To sum up, caution should be exercised when using eGFR as the sole marker for diagnosis of DKD.

LIMITATIONS OF ALBUMINURIA

Albuminuria is considered a marker of kidney damage, especially with glomerular dysfunction. An assay for detecting low concentration of urinary albumin was first described in the 1960s[20]. When compared with semi-quantitative method, it is more sensitive and specific for disease survey and monitoring. Similar to GFR, measurement of 24-h urine albumin is time-consuming, and adds little to prediction or accuracy[13,21]. Therefore, calculating UACR by checking albumin and creatinine levels in random spot urine samples is currently the standard of clinical practice. However, urinary albumin excretion may also increase for reasons other than DKD, such as physical activity, diet pattern, infection, fever, congestive heart failure, marked hyperglycemia, menstruation, and marked hypertension[22]. Therefore, the diagnosis of persistent albuminuria is based on abnormal UACR in two out of three specimens collected within a period of 3-6 mo[6].

A crucial point of clinical significance is the discordance between the presence of albuminuria and the decline in renal function. Perkins *et al*[23] reported the development of advanced CKD (GFR < 60 mL/min per 1.73 m^2) without concomitant progression of albuminuria in patients with T1DM enrolled in the Joslin Kidney Study. In the Third National Health and Nutrition Examination Survey (NHANES Ⅲ), a normal urinary albumin level was identified in 36% of the 1197 patients with T2DM who had advanced CKD[24,25]. In the United Kingdom Prospective Diabetes Study 74, only 49% of the patients with renal impairment had preceding albuminuria[26]. In the Developing Education on Microalbuminuria for Awareness of Renal and Cardiovascular Risk in Diabetes study, advanced CKD was noticed in 17% of those with normal UACR[27]. This discordance might be caused by the heterogeneous nature of renal injury, especially in T2DM. As mentioned above, albuminuria is a marker of glomerular dysfunction, which is characteristic of DKD in T1DM[28,29]. However, glomerulopathy is a less common pathogenesis in DKD of T2DM. In fact, tubulointerstitial and/or vascular lesions are sometimes the major histological changes[30-32]. Penno *et al*[33] described a strong association between prevalence of cardiovascular diseases and "non-albuminuric renal impairment", suggesting a predominance of macroangiopathy as the underlying renal pathology. Further studies are required to clarify this assumption.

ALTERNATIVE BIOMARKERS

Due to the limitations of eGFR and albuminuria in the early diagnosis of DKD, enormous efforts have been made to investigate and validate alternative biomarkers in recent decades. A tremendous amount of biomarkers have been evaluated for the diagnosis of DKD, and many studies have shown promising preliminary results (Table 1). However, large-scale studies are still required to validate the value of these biomarkers over and above that of eGFR and UACR.

Cystatin C (CysC) is a 13.3 kDa plasma protein freely filtered through the glomerulus. It does not re-enter the bloodstream in an intact form after being re-absorbed and catabolized by tubular cells[34]. Validation studies have showed that serum CysC levels are not affected by muscle mass, which is a major defect of creatinine, and are well-correlated with GFR[35-37]. In addition, CysC-based GFR estimation is more accurate than creatinine-based estimation when GFR remains > 60 mL/min per 1.73 m^2[38,39], suggesting that CysC might serve as a better marker of glomerular function in the early stages of DKD. However, a greater intra-individual variability compared to serum creatinine[37], together with a higher cost, should be considered before its clinical application.

Neutrophil gelatinase-associated lipocalin (NGAL) is a 25 kDa molecule which belongs to the lipocalin superfamily. It serves as a binder and transporter of small hydrophobic molecules, and a factor of innate antibacterial responses[40]. Urinary NGAL is closely related to the severity of renal impairment in various kidney disease. It is considered to play a protective role in such harmful conditions, as it is capable of promoting the proliferation and differentiation of renal cells[41]. Yang *et al*[42] reported that urinary NGAL correlated positively with serum CysC and creatinine levels, and inversely with GFR, whereas serum NGAL correlated negatively with serum CysC, in patients with T2DM. Furthermore, urinary NGAL has been shown to correlate positively with the severity of albuminuria in both T1DM[43] and T2DM[42] patients. In patients with short duration (less than 5 years) of T2DM, Fu *et al*[44] described a positive correlation between urinary NGAL and glomerular hyperfiltration. Such compelling evidences suggest the potential of NGAL as a novel biomarker for the early detection of DKD.

Kidney injury molecule 1 (KIM1) is a transmembrane protein with immunoglobulin-like and mucin domains in its ectodomain. Upregulated expression of KIM1 in renal tubules has been observed in ischemic, toxic, and proteinuric kidney diseases, suggesting its potential role as a marker of renal damage[45]. Similar to NGAL, elevated urinary KIM1 concentrations were identified in T2DM patients with glomerular hyperfiltration[44]. Nielsen *et al*[43] reported higher urinary KIM1 excretion in patients with T1DM than in healthy controls. Vaidya *et al*[46] showed that lower baseline concentration of urinary KIM1 was predictive of subsequent regression of albuminuria. These results indicate that the role of KIM1 in the early diagnosis of DKD is worth further investigation.

Table 1 Advantages of novel biomarkers in the early diagnosis of diabetic kidney disease

Biomarker	Validation study design	Sample size	Type of diabetes	Specimen	Advantages	Ref.
CysC	CO	52[38] 30[39]	2	Serum	Not affected by lean body mass Estimates more accurate than creatinine-based ones when GFR > 60 mL/min per 1.73 m^2	[35-39]
NGAL	CC	112	2	Urine	Indicator of glomerular hyperfiltration	[44]
KIM1	CC	112	2	Urine	Indicator of glomerular hyperfiltration	[44]
NAG	CC	434	1	Urine	Baseline level predicts development of DKD	[51]
	CC	946	2			[52]
8-oxodG	PC	396	2	Urine	Baseline level predicts development of DKD	[59]
Pentosidine	CC	434	1	Urine	Baseline level predicts progression of albuminuria	[51]
TNFR1/2	RC	628	1	Serum	Baseline level predicts development of advanced CKD	[65]
	RC	410	2			[66]

CysC: Cystatin C; NGAL: Neutrophil gelatinase-associated lipocalin; KIM1: Kidney injury molecule 1; NAG: N-acetyl-β-(D)-glucosaminidase; 8-oxodG: 8-oxo-7,8-dihydro-2′-deoxyguanosine; TNFR: Tumor necrosis factor receptor; CO: Case-only; CC: Case-control; PC: Prospective cohort; RC: Retrospective cohort; GFR: Glomerular filtration rate; DKD: Diabetic kidney disease; CKD: Chronic kidney disease.

N-acetyl-β-(D)-glucosaminidase (NAG) is a 130 kDa lysosomal enzyme located in the brush border of proximal renal tubular cells. Under normal conditions, NAG is excreted in low amounts in urine during the process of exocytosis. Elevated urinary NAG has been observed in various kidney diseases, suggesting a reflection of renal damage[47,48]. In patients with diabetes, increased excretion of NAG in urine has been identified to associate with the severity of albuminuria[49-51]. Despite inconsistency has been observed in the correlation between urinary NAG and glomerular hyperfiltration[44], results from the studies of Kern *et al*[51] and Hong *et al*[52] have indicated that higher baseline concentrations of urinary NAG were predictive of future development of DKD. On the other hand, lower baseline urinary concentration of urinary NAG was associated with the subsequent regression of albuminuria[46]. In addition to DKD, increased excretion of NAG in urine has also been reported to predict macrovascular complications in patients with T2DM[52-54].

Oxidative stress has been considered to play an important part in the pathogenesis of diabetic complications[55]. 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxodG) is an oxidized nucleoside - one of the major product of oxidative damage in nuclear and mitochondrial DNA[56]. Upon DNA repair, 8-oxodG is directly excreted into urine without further metabolization, so its urine concentration may serve as a generalized index of oxidative stress[57]. The study conducted by Hinokio *et al*[58] demonstrated a close correlation between urinary 8-oxodG excretion and the severity of microsvascular diabetic complications. In a 5-year cohort study of 532 Japanese patients with T2DM, baseline concentration of urinary 8-oxodG predicted subsequent development of DKD[59], indicating its potential as a predictive marker.

Hyperglycemia irreversibly modifies long-lived macromolecules by forming advanced glycation end products (AGEs), which cause qualitative and quantitative changes of the components of extracellular matrix. By affecting cell adhesion, growth, and matrix accumulation, AGE-induced changes are associated with the pathogenesis of diabetes complications[60]. One of the best chemically characterized AGEs found in human is pentosidine, which has been considered as a marker of formation and accumulation of AGEs[61]. Elevated urinary and plasma pentosidine levels were identified in T2DM patients with DKD[62]. Both urinary[51] and plasma[63] pentosidine levels have been demonstrated to correlate positively with the severity of albuminuria in patients with diabetes. In the study conducted by Kern *et al*[51], baseline urinary pentosidine excretion in patients with T1DM predicted the progression of albuminuria, with a seven-fold increase in risk for every 50% increase in urinary pentosidine.

Tumor necrosis factor (TNF)-α is a key mediator of inflammation and apoptosis. The signal transduction of TNF-α is commenced *via* two distinct receptors, TNF receptor (TNFR) 1 and TNFR2, which are presented in both membrane-bound form and soluble form in serum[64]. Serum levels of TNFR1 and TNFR2 were shown to correlate with GFR in patients with diabetes, and was independent of the status of albuminuria[64]. Recent studies in both T1DM[65] and T2DM[66] patients have indicated that plasma TNFR levels were capable of predicting the development of advanced CKD independently over 12 years of follow-up. These evidences suggest that serum concentrations of TNFR1 and TNFR2 may be utilized as predictors of DKD progression.

GENETIC SUSCEPTIBILITY

Genetic studies provide a powerful tool in the understanding of disease mechanisms. Emerging evidences have suggested that DKD is heritable[67-69]. Prior to the deployment of modern high-throughput technologies such as single nucleotide polymorphism microarray analysis and next-generation sequencing, linkage analysis had revealed variants on different chromosomal regions associated with DKD. For instance, variants on chromosome 18q have been identified to be associated with albuminuria and decreased renal function in different ethnic groups[70,71]. With the application of genome-wide association studies (GWASs) over the past decade, considerable progress has been made in the

understanding of genetic background of DKD. Genes such as engulfment and cell motility 1[72-77], FERM domain containing 3[78-81], cysteinyl-tRNA synthase[78,79,81], apolipoprotein L3-non-muscle myosin heavy chain 9[82,83] have been identified to be associated with the phenotypic presentations of DKD. Other risk loci have also been reported, yet data from different GWASs are not consistent[84]. Several fundamental problems remain to be solved before applying these results in clinical practice. First, genetic heterogeneity is always a major consideration when assessing the genetic background of any disease. Replication studies are essential for patients with DKD in different populations. Second, in most GWASs, DKD was defined as the co-existence of hyperglycemia and proteinuria; therefore, it is likely that these results are confounded by patients with renal damage due to causes other than diabetes. Last but not least, the actual functions of many genes which contain loci of risk are still unknown. Further studies are required to elucidate their roles in the pathogenesis of DKD.

EPIGENETIC MODIFICATIONS

Epigenetic modifications refer to DNA methylation, histone methylation, and histone acetylation, which alter the expression of a gene by changing its accessibility rather than nucleotide sequence[85]. In patients with diabetes, multiple factors, such as hyperglycemia, reactive oxygen species, and inflammation, can trigger epigenetic modifications[86]. Knowledge about the role of epigenetic modifications in the pathogenesis of DKD is currently very limited; however, since epigenetics is very sensitive to environmental factors, it is plausible that epigenetic imprints are responsible for the "metabolic memory" linked to diabetic complications[87]. Hasegawa *et al*[88] demonstrated that differentially methylated genes correlated with fibrogenesis in microdissected tubules obtained from patients with DKD. In a case-control study of 192 Irish patients with T1DM, Bell *et al*[89] reported that methylation at 19 CpG cites in several genes, including *UNC13B*, was associated with the time to development of DKD. Sapienza *et al*[90] identified 187 genes that were differentially methylated on at least two CpG sites among African American and Hispanic diabetic patients with ESRD. Intriguingly, many of these genes have been recognized previously through genome association or transcription profiling studies, and are associated with inflammation, oxidative stress, ubiquitination, fibrosis, drug metabolism, and development of DKD. These results suggest a very close connection between epigenetic modifications and genetic dysregulartions in the pathogenesis of DKD.

MICRORNA PROFILES

MicroRNAs (miRNAs) are small non-coding RNAs composed of 21-25 nucleotides that are produced by genes. By binding to target mRNAs, miRNAs induce degradation of RNAs or, more frequently, repression of protein translation[91]. Being packed within exosomes, miRNAs are stable in serum, plasma, and urine[92]. The stability makes miRNAs as potential candidate biomarkers for the non-invasive diagnosis of many diseases[93].

In vitro and *in vivo* studies have revealed the potential roles of miRNAs in the pathogenesis of DKD, especially in the early mesangial expansion stage. Changes in the expression of many miRNAs, such as miR-192[94-97], miR-216a[98], miR-377[99], miR-29c[100], miR-200b/c[101], miR-21[102], miR-1207-5p[103], miR-200a[104], and miR-23b[105], have been identified to be involved in the process of extracellular matrix expansion and fibrosis, interaction with transforming growth factor β and other pro-fibrotic genes. Long *et al*[106] identified miR-93 as a novel regulator of vascular endothelial growth factor in *in vitro* and *in vivo* experimental models under hyperglycemic conditions. Fu *et al*[107] described a significant reduction of endogenous miR-25 in rat mesangial cells treated with high glucose concentrations and in the kidneys of diabetic rats associated with increased nicotinamide adenine dinucleotide phosphate hydrogen oxidase (NOX) activity characterized by high NOX4 expression levels. Zhang *et al*[108] reported that over-expression of miR-451, which targets tyrosine3-monooxygenase/tryptophan 5-monooxygenase activation protein, zeta and p38 mitogen-activated protein kinase signaling pathways, resulted in reduced glomerular mesangial cell proliferation *in vitro* and *in vivo*. These experimental findings are summarized in Table 2.

The urinary and serum miRNA in patients with DKD have also been profiled. In T1DM patients with albuminuria, Argyropoulos *et al*[109] showed underexpression of urinary miR-323b-5p, miR-221-3p, miR-524-5p, and miR-188-3p, whereas miR-214-3p, miR-92b-5p, hsa-miR-765, hsa-miR-429, miR-373-5p, miR-1913, and miR-638 were overexpressed. On the other hand, an elevation in urinary miR-130a and miR-145 levels, with a reduction in miR-155 and miR-424, were reported by Barutta *et al*[110] in a similar setting. In patients with T2DM, Peng *et al*[111] described a positive correlation between urinary miR-29 levels and the severity of albuminuria.

Expression of miRNAs was also measured in venous blood from Chinese T2DM patients with and without DKD. Using a microarray-based approach, Zhou *et al*[112] confirmed the downregulation of miR-let-7a in the patients with DKD. Intriguingly, the authors also observed that the distribution of a specific variant within *let-7a* (rs1143770) was significantly higher in patients with diabetes than in healthy controls. These results are summarized in Table 3.

PROTEOMIC SIGNATURES

Proteomics is defined as "the knowledge of the structure, function, and expression of all proteins in the biochemical or biological context of organisms"[113]. The most attractive feature of proteomics is that it allows the monitoring of patterns of multiple urine and plasma proteins simultaneously. Considering the sophisticated

Table 2 *In vitro* and *in vivo* renal cell models demonstrating the potential involvement of miRNAs in development of diabetic kidney disease

miRNA	Species	Specimen	miRNA expression	Mechanism of action	Ref.
miR-192	Mice/Rat	M, Te, KT	Inconsistent results	Interaction with TGFβ-associated and other pro-fibrotic genes	[94-96]
	Human	Te, KT	Reduced		[97]
miR-216a	Mice	M, KT	Elevated		[98]
miR-377	Mice	M, KT	Elevated		[99]
	Human	M			
miR-29c	Mice	P, KT	Elevated		[100]
miR-200b/c	Mice	M, KT	Elevated		[101]
miR-21	Mice	KT	Elevated		[102]
	Human	Te			
miR-1207-5p	Human	P, M, Te	Elevated		[103]
miR-200a	Rat	Te	Reduced		[104]
	Mice	KT			
miR-23b	Mice	KT	Reduced		[105]
	Human	Te, HEK-293A			
miR-93	Mice	P, En, KT	Reduced	Regulation of VEGF expression	[106]
miR-25	Rat	M, KT	Reduced	Regulation of NOX4 expression	[107]
miR-451	Mice	M, KT	Reduced	Targeting YwhaZ and p38 MAPK signaling pathways	[108]

M: Mesangial cells; Te: Tubular epithelial cells; KT: Kidney tissue; P: Podocytes; En: Endothelial cells; TGFβ: Transforming growth factor β; VEGF: Vascular endothelial growth factor; NOX4: Nicotinamide adenine dinucleotide phosphate hydrogen oxidase 4; YwhaZ: Tyrosine3-monooxygenase/tryptophan 5-monooxygenase activation protein, zeta; MAPK: Mitogen-activated protein kinase; HEK-293A: Human Embryonic Kidney-293A cells.

nature of DKD, especially in patients with T2DM, it is plausible that early diagnosis of this disease, which relies only on a single biomarker, might eventually fail to reach optimal sensitivity and specificity[114]. The role of proteomics in the early diagnosis of DKD, therefore, is worthy of further evaluation.

DN65 is a panel composed of 65 urinary biomarkers, many of which are fragments of type Ⅰ collagen. In the study conducted by Rossing *et al*[115], DN65 was capable of distinguishing between diabetic patients without albuminuria from those with DKD. It was also proved to be sensitive and specific in distinguishing DKD from CKD of other etiologies, as well as predicting the progression toward overt DKD in patients with diabetes who had albuminuria over 3 years. First described by Good *et al*[116] in 2010, CKD273 is another panel of 273 urinary peptides and proteins capable of identifying CKD of any cause with excellent sensitivity and specificity. In a cohort of 35 patients with diabetes, Zürbig *et al*[117] showed that the CKD273 classifier was capable of detectingthose who were at risk of DKD progression up to 5 years prior to development of overt albuminuria. In the Prevention of Renal and Vascular End-stage Disease (PREVEND) cohort, Roscioni *et al*[118] showed that the baseline CKD273 classifier score was independently associated with the progression of albuminuria. In urine samples obtained from 165 patients with T2DM at 9 different centers, Siwy *et al*[119] demonstrated that the classifier could identify DKD patients with high consistency.

METABOLOMIC SIGNATURES

Metabolomics refers to the identification of low molecular weight intermediate and end-products of cellular functions in a biological sample with nuclear magnetic resonance and mass spectrometry-based profiling techniques[120,121]. As metabolome represents the complete collection of metabolites in an organism, understanding the perturbations in human metabolome might help with early unveiling of the pathological changes in disease processes.

Several studies have assessed the potential of metabolomics in diagnosis of DKD (Table 4). Han *et al*[122] described the diverse profiles of plasma fatty acids in different stages of DKD. In 82 patients with T2DM, Zhu *et al*[123] demonstrated that a panel of six plasma phospholipids was capable of distinguishing between patients with and without DKD. In 78 patients with diabetes, Hirayama *et al*[124] identified a panel of 19 serum metabolites correlated significantly with UACR. A multiple logistic regression model composed of the five best performing markers (including γ-butyrobetaine, symmetric dimethylarginine, azelaic acid, and two unknowns) yielded remarkable sensitivity and specificity for the diagnosis of DKD. Sharma *et al*[125] quantified 94 metabolites in urine obtained from healthy control, diabetic patients with and without DKD. A decrease in the urine levels of 13 metabolites, many potentially related to mitochondrial function, was found to be associated with DKD. Pena *et al*[126] described the different metabolomic profiles in the urine and plasma samples from the T2DM cohort of the PREVEND study. Differences were observed in the levels of plasma histidine, butenoylcarnitine, as well as urine hexose, glutamine, and tyrosine, between those who with and without albuminuria. Adding these metabolites to a predictive model composed of baseline urinary albumin excretion and eGFR improve risk estimation for the progression of albuminuria. In the T2DM cohort of the Joslin Kidney Study, Niewczas *et al*[127] identified a panel of 5 plasma metabolites capable of predicting progression toward ESRD, which was independent of UACR, eGFR, and hemoglobin A_{1c}. Although

Table 3 Urinary and serum miRNA profiles in patients with diabetic kidney disease

Type of diabetes	Specimen	miRNA expression		Ref.
1	Urine	Decreased miR-323b-5p, miR-221-3p, miR-524-5p, miR-188-3p	Increased miR-214-3p, miR-92b-5p, hsa-miR-765, hsa-miR-429, miR-373-5p, miR-1913, miR-638	[109]
1	Urine	Decreased miR-155, miR-424	Increased miR-130a, miR-145	[110]
2	Urine	miR-29 expression positively correlated to the severity of albuminuria		[111]
2	Blood	Reduced expression of miR-let-7a		[112]

Table 4 Applications of metabolomics in the diagnosis of diabetic kidney disease

Specimen	Panel	Application	Ref.
Plasma	Fatty acids C10:0, C12:0, C14:0, C16:1n-9, C16:0, C18:2, C18:1n-9, C18:1n-11, C18:0, C20:4, C20:5, C20:3, C20:2, C20:0, C22:6	Diverse profiles in different stages of DKD	[122]
Plasma	Phospholipids C18:2-LPC, C16:0/18:1-PE, pC18:0/20:4-PE, C18:0/22:6-PI, C18:0/18:0-PS, dC18:0/20:2-SM	Diagnosis of DKD	[123]
Serum	γ-butyrobetaine, SDMA, azelaic acid, MID 114, MID 127	Diagnosis of DKD	[124]
Urine	3-hydroxy isovalerate, aconitic acid, citric acid, 2-ethyl 3-OH propionate, glycolic acid, homovanillic acid, 3-hydroxy isobutyrate, 2-methyl acetoacetate, 3-methyl adipic acid, 3-methyl crotonyl glycine, 3-hydroxy propionate, tiglylglycine, uracil	Reduced expression in DKD patients	[125]
Plasma and urine	Plasma: Histidine, butenoylcarnitine Urine: Hexose, glutamine, tyrosine	Addition to the original predictive model improved risk estimation for albuminuria progression	[126]
Plasma	P-cresol sulfate, phenylacetylglutamine, myoinositol, pseudouridine, urate	Predicting progression toward ESRD	[127]

LPC: Lysophosphatidylcholine; PE: Phosphatidylethanolamine; PI: Phosphatidylinositol; PS: Phosphatidylserine; SM: Sphingomyelin; SDMA: Symmetric dimethylarginine; MID: Metabolite ID; DKD: Diabetic kidney disease; ESRD: End-stage renal disease.

these results seems promising, the complexity of the analysis techniques and the incomplete coverage of the human metabolome at present are problems than may need to be addressed before the application of metabolomics in everyday practice.

CONCLUSION

The development of DKD involves the dysfunction and damage of different renal tissues in multiple stages. Due to the complex nature of this disease, whether there is a "universal" biomarker is questionable. With extensive validations, albuminuria and eGFR are currently the standard diagnostic criteria for DKD. Nonetheless, the abilities of these markers to detect tissue damage and functional change in the early stage are limited. With the increasing understanding of pathogenesis and promising preliminary data, applying the information generated from the studies of novel biomarkers, genomic, and proteomic profiles to assist in the early diagnosis of DKD has gradually become plausible. An integration of the "traditional" and "next-generation" markers might be more practical in everyday settings, considering the financial and technical requirements of these novel assays. To sum up, large longitudinal cohort studies are still required to validate the abilities of the aforementioned novel early diagnosis and prediction techniques.

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