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Trends in laboratory testing practice for diabetes mellitus

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ABSTRACT

Background

India, with diabetes mellitus (DM) prevalence of nearly 7%, contributes 20% of the DM population in the world. The diagnosis and management of DM is largely dependant on laboratory parameters. We aimed to survey the laboratory testing practices for DM in this country.

Methods

A survey of 890 practising Laboratorians in India was conducted through Survey Monkey.

Results

A total of 310 (35%) complete responses were received. The majority of respondents worked in academic institutions, public hospital laboratories and private hospital laboratories. HbA1c was approved for diagnosis in 75% of laboratories. The HbA1c method was NGSP (National Glycohaemoglobin Standardisation Programme) certified in 70% of laboratories only. Oral glucose tolerance testing (OGTT) was recommended for diagnosis of gestational diabetes (GDM) in 56%

of respondents. Fifty-nine percent respondents recommended an early morning urine sample for microalbuminuria testing whilst 39% and 2% opted for 24 hour urine and timed overnight sample respectively. Sixty-six percent participated in proficiency testing (PT) for both glucose and HbA1c. Twelve percent and 4% respondents respectively participated in PT for glucose only and HbA1c only, and 9% participated in PT for neither.

Conclusions

Based on the above survey we recommend that Scientific bodies and Professional Associations in India should educate Laboratorians to adopt NGSP certified methods for HbA1c testing and morning spot sample for microalbuminuria testing. DIPSI (Diabetes in Pregnancy Study Group in India) guidelines for diagnosis of Gestational diabetes since it is a simple, single step procedure, non-fasting, cost effective, feasible method should be implemented.

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INTRODUCTION

There are close to 66.8 million patients with diabetes mellitus (DM) in India, which represent nearly 7% of the country's adult population. [1] Every fifth diabetic in the world is from India. [2] Therefore, it is imperative that we understand the laboratory testing practices for DM in India, since the diagnosis and management of DM both rely heavily on laboratory parameters. [3] Understanding the trends in laboratory testing of DM helps us identify the lacunae and gaps in knowledge as well as barriers in the optimal management of DM. Based on this, recommendations can be made by associations and professional bodies to fill in the gaps in knowledge. Identifying the lacunae in the laboratory testing practices would also help health administrators to formulate policies and allocate resources, so as to remove the barriers and to bridge the gap in knowledge.

METHODS

To understand the trends in laboratory testing practice in India a survey was conducted by using the survey monkey app. A survey was designed under the aegis of Asia Pacific Federation of Clinical Biochemistry and sent by Whats app to approximately 890 respondents between July and October 2018. Participants whose mobile numbers were not available were sent the survey on their respective emails. Access to mobile contact numbers as well as emails of participants were obtained from the registries of Association of Medical Biochemists of India (AMBI) and Association of Clinical Biochemists of India's (ACBI) respective websites which had listed contact numbers as well as emails of their members. For 150 Biochemists and Pathologists whose mobile numbers were not available in the respective member directories were sent the Survey Monkey link as an attachment to their emails. Due permission of the Presidents of the associations were obtained before accessing the contact numbers and emails.

The survey questions are depicted in Table 1, on the next page. The responses were collected from the Survey Monkey website, collated and analysed.

RESULTS

Maximum responses were received between July and August 2018. Three hundred and thirteen (31.3%) of the recipients responded. Of these responses, 310 surveys were complete and three were incomplete. The results of the survey are depicted in the Bar graphs below (Figure 1).

Some 3% of respondents use mmol/L as unit for reporting blood glucose. One fourth of the respondents reported that HbA1c was not used in their hospitals/laboratories for diagnosis of

Table 1 Survey questions

1. What units do you use for reporting blood glucose?

a) mmol/L

b) mg/dL

2. Is HbA1c approved for diagnosis of Diabetes in your country?

a) Yes

b) No

3. Is HbA1c used for diagnosis of diabetes in your laboratory/hospital?

a) Yes

b) No

4. Is your HbA1c method NGSP (National Glycohaemoglobin Standardization Programme) certified?

a) Yes

b) No

5. For the diagnosis of diabetes mellitus, which of the following diagnostic cut-offs are reported by your Laboratory?

a) HbA1c > 6.5% (48 mmol/mol)

b) Fasting plasma glucose > 126 mg/dL (7.0 mmol/L)

c) 02 hour post glucose load glucose > 200 mg/dL (11.1 mmol/L) during an OGTT

d) Symptoms of hyperglycemia and random plasma glucose > 200 mg/dL (11.1 mmol/l)

6. Is OGTT routinely recommended for the diagnosis of Gestational Diabetes?

a) Yes

b) No

7. For monitoring of diabetes, which of the following thresholds of HbA1c is reported as good control?

a) 7%

b) 6.5%

8. For testing microalbuminuria, which of the following urine samples is recommended?

a) Early morning spot urine

b) 24 hour urine

c) Timed overnight urine

9. Are Laboratories required to participate in PT program for testing glucose and HbA1c?

a) Glucose only

b) HbA1c only

c) Both

d) None

e) If yes, does your Laboratory participate in PT program?

10. Which type of Laboratory do you work?

a) Public hospital

b) Private Hospital

c) Public stand alone

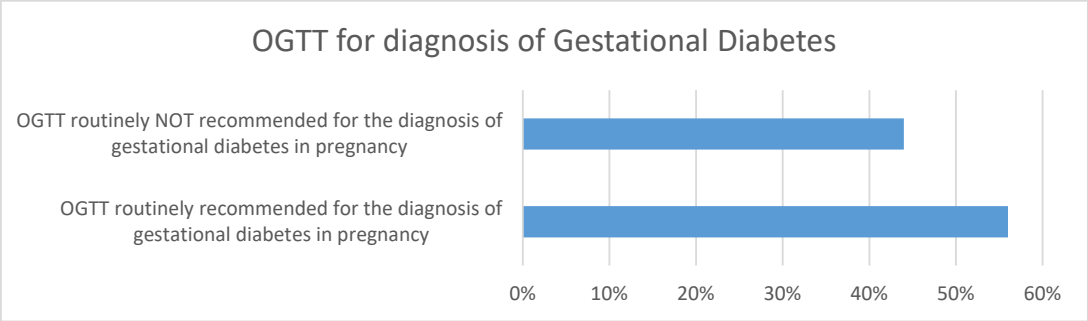
d) Private stand alone

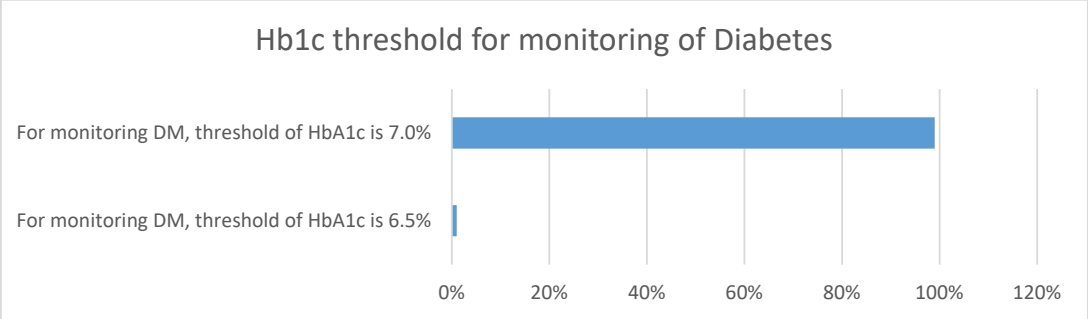
e) Academic university

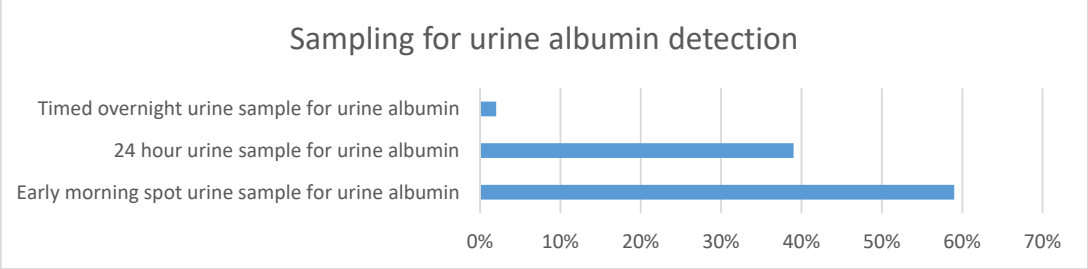
f) Research Lab

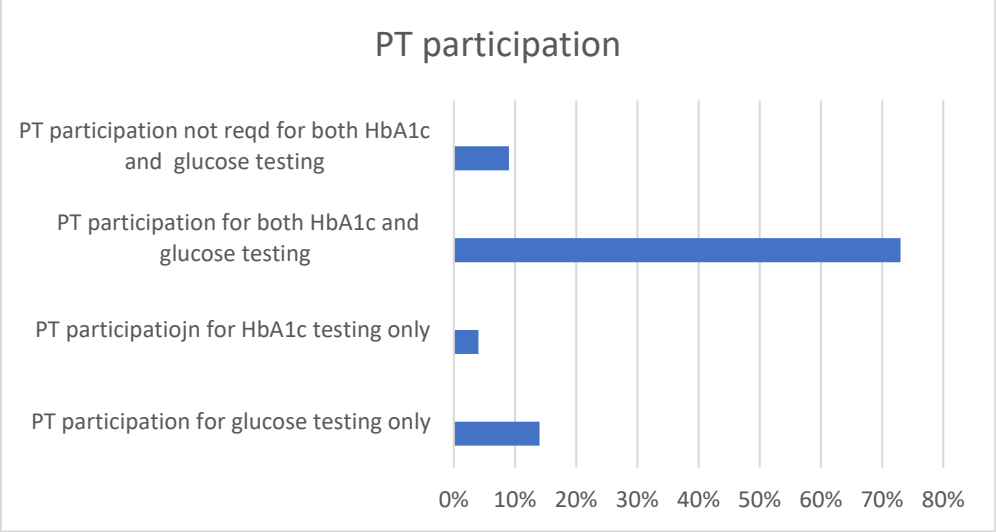
DM. Thirty percent of respondents stated that their method for estimation of HbA1c was not NGSP certified. Criteria used most commonly by respondents (83%) for the diagnosis of DM was fasting >126mg/dL followed by post prandial glucose of 200 mg/dL reported by 71% respondents. Only 58% respondents used random plasma glucose >200mg/dl as a diagnostic cut

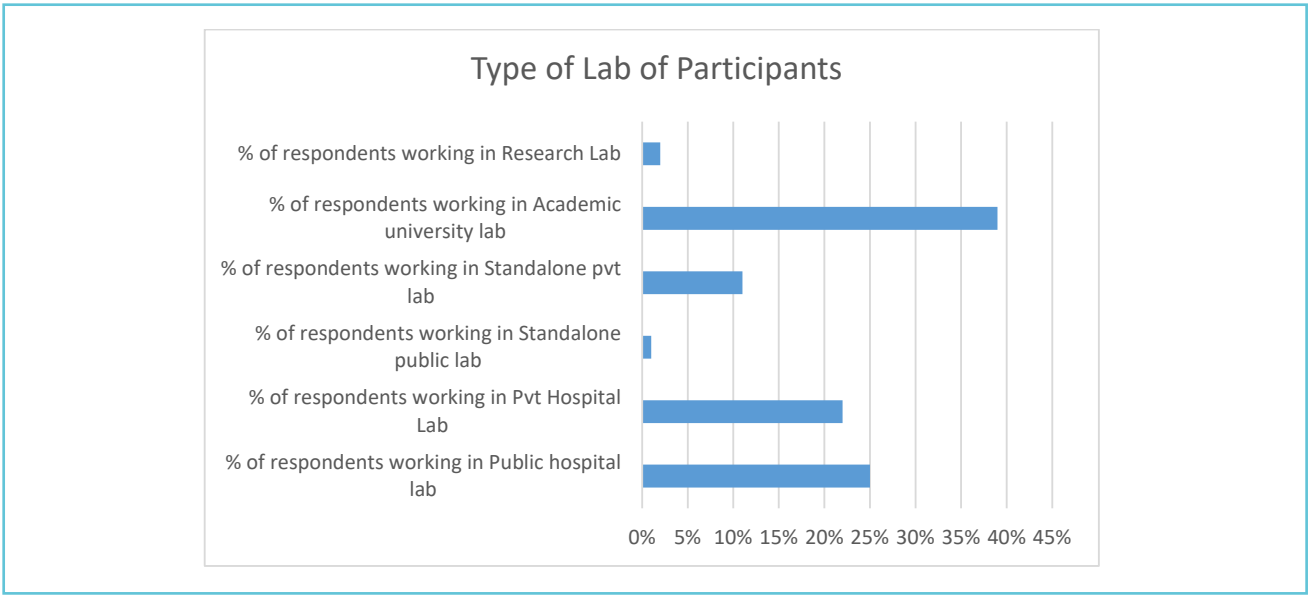
Figure 1 **Survey results**


OGTT for diagnosis of Gestational Diabetes
OGTT routinely NOT recommended for the diagnosis of gestational diabetes in pregnancy
OGTT routinely recommended for the diagnosis of gestational diabetes in pregnancy
0%
10%
20%
30%
40%
50%
60%


Hb1c threshold for monitoring of Diabetes
For monitoring DM, threshold of HbA1c is 7.0%
For monitoring DM, threshold of HbA1c is 6.5%
0%
20%
40%
60%
80%
100%
120%


Sampling for urine albumin detection
Timed overnight urine sample for urine albumin
24 hour urine sample for urine albumin
Early morning spot urine sample for urine albumin
0%
10%
20%
30%
40%
50%
60%
70%


PT participation
PT participation not reqd for both HbA1c and glucose testing
PT participation for both HbA1c and glucose testing
PT participatiojn for HbA1c testing only
PT participation for glucose testing only
0%
10%
20%
30%
40%
50%
60%
70%
80%



off for the diagnosis of DM. Only 56% respondents reported that OGTT was recommended for the diagnosis of gestational DM. A vast majority of respondents (99%) reported that the HbA1c threshold for the control of DM is 7%. For estimation of microalbuminuria (MAL), 59% preferred early morning urine sample followed by 39% who preferred a 24 hour urine collection. Two thirds of respondents reported that their laboratories participated in proficiency testing (PT) for both Glucose and HbA1c testing whereas 12% and 8% respectively reported that their laboratories were participating in PT for glucose andHbA1c only.

The majority of participants were from academic university, public hospital and private hospital Laboratories.

DISCUSSION

This survey was performed in order to obtain a snapshot of the laboratory testing practices for DM throughout India. A response rate of 31% is not optimal but the absolute numbers are large and does provide an indication of the practices being followed in this country. A large proportion of our respondents were from academic university laboratories, which service major teaching hospitals, followed by public and private hospital laboratories.

Respondents almost unanimously reported blood glucose in mg/dL although standard international unit for reporting blood glucose is mmol/L. Some countries such as USA and Germany report glucose in mg/dL like India but in others such as UK it is reported in mmol/L. International professional organisations such as IFCC (International Federation of Clinical Chemistry) in collaboration with various national bodies/associations may recommend all countries to report in SI units. However, there are no existing Indian guidelines to this effect.

Whilst HbA1c is now internationally approved for the diagnosis of DM, a sizeable minority of hospitals in India are not using it for this purpose and a similar proportion of laboratories are not offering HbA1c testing for this purpose. Herein, comes the role of Indian professional associations to spread awareness among Biochemists and Pathologists to enable them to offer HbA1c for the diagnosis of DM as has been recommended as well as educate clinicians. One of the reasons, it is not used for diagnosis is possibly resource limitations in public laboratories who were the majority of our

respondents where the cheaper alternative of estimation of blood glucose is undertaken for the diagnosis of DM.

Based on the survey above, it is recommended that Biochemists /Pathologists be made aware of the National Glycohemoglobin Standardization Program (NGSP) certification of HbA1c estimation methods. This will help in harmonisation of HbA1c methods across laboratories and different testing platforms. The lack of comparability of glycated haemoglobin (GHb) test results across methods and laboratories previously posed a major hurdle to a meaningful implementation of specific guidelines for DM care. [4] NGSP was implemented to enable laboratories to report DCCT (Diabetes Control and Complications Trial) traceable GHb/HbA1c results. Over the years, the number of NGSP certified methods and laboratories traceable to the DCCT have increased remarkably. By 2002, 98% of surveyed laboratories (n ~ 2000) reported GHb results as HbA1c or equivalent compared to 50% in 1993. [4] Little RR in his study in 2002 had reported that 97% of laboratories used an NGSP-certified method and only 3% were not following NGSP certified testing.[4] Our survey shows that 30% respondents were not reporting HbA1c by NGSP certified methods. This clearly highlights the role of spreading awareness among laboratorians to use NGSP certified methods for HbA1c estimation. For certified methods in 2002, inter laboratory CVs were <5%. In 2002, for all certified methods, the mean HbA1c value (%) was within 0.8% of HbA1c from the NGSP target at all HbA1c concentrations. [4] Hence, ensuring that all laboratories estimate HbA1c with NGSP methods will go a long way in harmonisation of HbA1c methods. IFCC has developed a robust reference method which is more specific for HbA1c. [5] NGSP has now adopted this IFCC method as the reference system. Since the IFCC method is specific for HbA1C and it does not measure other haemoglobin sugar complexes the result is 10-40% lower than the NGSP values depending on the levels of glycated haemoglobin. There is a linear relationship between the IFCC and NGSP values. The equation used to convert NGSP units to the SI units is as follows:

HbA1c SI unit (mmol/mol) = 10.93 HbA1c NGSP unit (%) − 23.50. [6]

All laboratorians engaged in HbA1c testing should apprise themselves with the factors interfering with their test methodology. Factors which are known to commonly decrease HbA1c values are acute haemorrhage, haemolytic anemias and iron therapy in pregnancy. Factors which increase HbA1c are Iron deficiency anemia, late pregnancy (due to an iron deficient stage). [7] Selvaraj N et al in their study have proposed that RBCs incubated with Malondialdehyde and glucose registered a higher HbA1c when compared with RBCs incubated with glucose alone. [6] They pretreated RBCs with taurine and choline which decreased the production of MDA and showed a decrease in HbA1c. [8] They therefore propose that MDA has a role in increasing the glycation of haemoglobin. The exact mechanism of how MDA causes increased glycation of Haemoglobin is however not clear. Mawatari S et al in their study have however not found any difference in the levels of MDA in patients with high HbA1c and those with low HbA1c. [9] The role of MDA therefore in causing increased glycation of Haemoglobin is highly controversial. Most diabetics develop diabetic nephropathy as a complication of DM. They have substantial amount of carbamylated haemoglobin which occurs due to the non-enzymatic addition of urea to haemoglobin. Carbamylated haemoglobin is known to interfere with HbA1c levels, based on the method which is being used for the estimation of HbA1c it may increase or decrease the levels of HbA1c. [7]The effects of anemia of chronic disease and erythropoietin on glycation of Haemoglobin (which occurs in CKD) are

difficult to ascertain which are based on methods used to estimate HbA1c.

HbS and HbC, alter the structure of Hb close to it's N terminus, affecting methods that depend on detecting structural differences like immunoassays. In contrast, HbD and HbE, do not cause structural alterations near the N-terminus and hence do not cause interference in immunoassays. Interference with ion-exchange methods can be seen in any of the four variants described as they alter the charge of Hb molecule. Assays utilizing immunoturbidimetry and boronate affinity chromatography are usually not affected by the presence of Hb variants. [10]

The HbA1c target for control of DM has been recommended to be at 7% by various bodies (American Diabetes Association/International Diabetes Federation). However, it has been recommended by NGSP that the target could be set at 8% for patients with history of hypoglycemia, co morbidities or expected life span of less than twenty years, patients with major visual/cognitive impairments leading to impaired self-management. [11]

Unless patient is symptomatic with random glucose > 200 mg/dL or patient is in a hyperglycemic crisis test for diagnosis should not be repeated. Either the same test or a different test should be repeated using a different sample. If two different tests are diagnostic then the diagnosis is confirmed. If the results of two different tests are discordant then the test which is diagnostic should be repeated. [3]

Keeping in view, that Asian women have a significantly higher risk of developing glucose intolerance compared to Caucasian women, universal screening for early detection of GDM should be offered to all pregnant women. [12] Most obstetricians in India used the DIPSI (Diabetes in Pregnancy Study group in India) guidelines for diagnosis of Gestational diabetes since it is a simple, single step procedure, non-fasting, cost effective, feasible method. [13]The DIPSI guidelines look at glucose values post 75 g glucose load at 02 hour. The values of 200 and 140 mg/dl are diagnostic of DM and Gestational diabetes Mellitus respectively. An additional criteria which has been introduced is a post 75 g glucose load 2 hour value of 120 mg/dL which is indicative of DGGT (Decreased Gestational Glucose Tolerance). The advantages of DIPSI criteria are that the patient irrespective of meal status can be administered 75 g oral glucose. It serves both as a screening and diagnostic test.[14] DIPSI guidelines suggest that patients be screened every trimester since it has been shown that fetal beta cells respond to maternal glycaemic levels by 12 weeks of gestation. If found negative in the first trimester, screening should be performed at 24-28 weeks and thereafter finally at 32-34 weeks. [15] Present ADA recommendations of screening at 24-28 weeks are late. Methods of diagnosing GDM earlier will decrease the co morbidity of GDM. Gynaecologists, endocrinologists and Biochemists must be educated to administer OGTT in all cases of pregnancy in the first trimester itself to diagnose GDM earlier to ensure favourable outcome in both the mother as well as the foetus.

Mahalakshmi et al, in their survey of clinicians, surveyed 3841 doctors, of which 2020 comprised of a heterogeneous group of Physicians, Diabetologists/Endocrinologists and of which 1821 were Obstetricians and Gynaecologists. A diverse trend in the management of Gestational Diabetes by both these groups was observed. Thirty seven percent of Gynaecologists reported using the Diabetes in Pregnancy Study Group India (DIPSI) criteria, 25% the World Health Organisation (WHO) 1999 criteria, 24% the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria, and 15% the American Diabetes Association (ADA) 2- step method (50 g Glucose Challenge Test followed by 100 g 3 h Glucose Tolerance Test with

the cut offs proposed by Carpenter and Coustan or by the National Diabetes Data Group. [16] Among the Physicians/Endocrinologists 29% reported using the DIPSI criteria, 23% the WHO 1999 criteria, 19% the IADPSG criteria, and 29% the ADA criteria. From this data it is evident that the single most common criteria popular among clinicians in India is the DIPSI criteria.

Clinicians should endeavour to follow the same guidelines IADPSG/ WHO/ADA/DIPSI across the country to bring in standardisation in the testing of GDM across the country so that similar management protocols can be followed universally. ACBI/AMBI may play a role in attempting to harmonize practice nationally in collaboration with professional clinical associations. This will obviate any kind of retesting when a patient changes her centre and therefore will lead to conserving financial resources, manpower and time.

Microvascular complications are a dreaded sequel of DM. For the diagnosis of microvascular complications of DM, assessment of MAL is recommended. MAL is a misnormer and hence urine albumin creatinine ratio would be a better method of assessing early diabetic nephropathy. Urine microalbuminuria & urine albumin creatinine ratio show a very good correlation 0.509. [17] Various methods of evaluating microalbuminuria are immunonephelometry, immunoturbidimetry, Radio Immunoassay. Immunoturbidimetry assays are good screening assays for assessing nephropathy. [18] Babazono et al in their study titled “Definition of MAL based on first morning sample and random morning urine sample in diabetic patients” studied a total of 668 individuals with and without nephropathy with 95% of patients having type 2 diabetes with a mean age of 58 +/- 12 yrs. The cohort consisted of 289 women 379 men. All patients submitted first morning sample and also random morning samples. Seventy five percent of random samples were collected between 0830 to 1200 PM. They have found a correlation of r = 0.859, between first morning and random morning urine samples. The cut off for first morning sample was 30-300 mg/g and 51-391mg/g for random morning sample. On applying the above diagnostic cut offs, 20% of patients were diagnosed to have MAL when early morning urine sample was submitted and 35% were diagnosed to have MAL when random spot urine was submitted. [19] Miller WG et al in their study have shown that morning fasting sample is preferred by 81% people, followed by 14% and 5% patients who submitted timed overnight and 24 hour sample. [20] In our survey, 39% of laboratories preferred 24 hour urine sample which is much higher than that reported by Miller et al. Collection of a 24 hour urine sample for estimation of albumin creatinine ratio, is a very tedious procedure for the patient which entails cumbersome collection procedure with a designated container and preservative which decreases patient compliance and introduces a vast array of preanalytical variables in the estimation of albumin creatinine ratio. Hence, it should be emphasised here that random urine samples are good enough for estimation of albumin creatinine ratio even though early morning samples are ideal. ADA as well as NKD (National Kidney Foundation) have recommended ACR in a random spot urine sample for convenience. [21,22] Spot random sampling definitely will go a long way in increasing patient compliance and therefore is a better testing strategy.

Harmonisation of albumin measurement in urine is not an easy task since there are a multitude of methods available. Also compounding the problem is the fact that, there is no reference material for traceability studies. Commutability of available reference material also needs to be addressed. JSCC (Japanese Society for Clinical Chemistry) and JCCLS (Japanese Committee for Clinical Laboratory Standards) have coordinated the development of a new urine albumin

secondary Reference material for this purpose. [23] Age, gender and ethnicity specific reference intervals may be appropriate for the interpretation of reports but are not available.

The role of Professional bodies like the NABL (National Accreditation Board for Laboratories) has gone a long way towards increasing awareness amongst laboratorians to participate in Proficiency Testing (PT) programmes. Most laboratories in India, participate in the CMC (Christian Medical College), External Quality Assurance Scheme due to it's affordability even by small standalone labs. Some also participate in International PT programmes.

Awareness is required among laboratorians to choose NGSP certified methods for the estimation of glycated Haemoglobin in their respective Laboratories. Spot random urine samples are acceptable for estimation of MAL and patients may be spared the trouble of collecting 24-hour urine sample for estimation of MAL. Gynaecologists should start screening for GDM from the first trimester itself. National associations & scientific bodies have a major role in educating & sensitizing laboratorians in this regard and ensuring harmonized practices nation-wide. These measures will go a long way in the ease of detection and management of DM. Other developing nations in the Asia Pacific region like Pakistan, Bangladesh, Nepal, Bhutan, Sri Lanka and Phillipines could also use this survey as a template to formulate their own policies/guidelines in the diagnosis and management of DM since the socioeconomic conditions prevailing and existing health infrastructure in the neighbouring countries are very similar to India.

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Authors' contributions

MB: Execution of survey, manucript preparation

SV: Conceptualising the survey, Proof reading of the manuscript

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