DETERMINATION OF FREQUENCY OF A NOVEL DIAGNOSTIC CATEGORY OF HYPERGLYCEMIA I.E. IMPAIRED RANDOM GLUCOSE IN PREVIOUSLY UNKNOWN PATIENTS OF PREDIABETES AND DIABETES MELLITUS

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ABSTRACT

Objective: To determine the frequency of normoglycemia (NG), prediabetes and diabetes mellitus (DM) among patients having impaired random glucose (IRG) and establish the optimum cutoff of impaired random glucose for the diagnosis of diabetes and prediabetes.

Study Design: Cross sectional study.

Place and Duration of Study: Armed Forces Institute of Pathology Rawalpindi and Combined Military Hospital Quetta, from Nov 2016 to Nov 2018.

Methodology: Healthy individuals of both genders undergoing investigation for diabetes mellitus were enrolled through non probability consecutive sampling while patients with diabetes, pregnant, hospitalized, using concomitant medications (corticosteroids, immunosuppressive, chemotherapy) and those unable to complete oral glucose tolerance test (OGTT) were excluded. Random plasma glucose (RPG) was determined and patients having impaired random glucose underwent oral glucose tolerance test, analysis being done on ADVIA1800® using hexokinase methodology.

Results: Among the 280 study participants, majority were female {156 (57.5%) vs 124 (44.3%) male}. Mean age in male and female patients was 33.625 ± 3.34 years vs 35.150 ± 2.79 years with *p*-value 0.50 while mean IRG was 7.12 ± 1.47 vs 6.90 ± 1.17 mmol/L respectively with *p*-value 0.16 (statistically insignificant). Oral glucose tolerance test results showed NG in 61.8% (173), prediabetes in 24.6% (69) while diabetes was found in 38 (13.6%) patients. Optimal impaired random glucose cutoff value for diagnosis of diabetes was found 7.45 mmol/L (AUC 0.956 [CI 0.927-0.984], *p*<0.001, sensitivity 94.7%, specificity 74.4%), however, same cut-off value showed impaired random glucose as fair diagnostic test for prediabetes (AUC 0.771 [CI 0.717-0.825], *p*<0.001, sensitivity 72.5%, specificity 77.3%).

Conclusion: Random plasma glucose helps diagnose patients at risk of prediabetes and diabetes who may otherwise not be identified. Impaired random glucose ≥7.45 mmol/L was found optimal to initiate definitive testing.

Keywords: Diabetes mellitus, Frequency, Glucose tolerance test, Prediabetes.

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INTRODUCTION

Diabetes mellitus (DM) is one of the most common chronic diseases occurring in epidemic proportions¹, requiring multifactorial risk-reduction strategies beyond glycemic control. The international diabetic federation (IDF) has predicted that the number of individuals with DM will increase from 425 million in 2015 to 629 million in 2045 while causing 5.1 million deaths and consuming \$727 billion in 2017². DM is a major national health problem and Pakistan is among top ten countries of the world having greatest number of people having diabetes. According to the Pakistan National Diabetes Survey (PNDS), 9.3% males and 11.1% females suffer from DM while other surveys showed slightly higher proportions³.

Approximately one third of the patients with diabetes and 90% with prediabetes remain undiagnosed until complications occur². Prediabetes not only predisposes to DM but also itself is associated with increased risk of stroke, coronary artery disease, peripheral vascular disease, dyslipidemia, hypertension and obesity⁴. American diabetic association (ADA) recommends early

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detection of DM and prediabetes as effective lifestyle/pharmacological interventions available can prevent progression of disease and its complications conserving tremendous amount of resources5. Current tests to diagnose DM include blood glucose-based tests and glycated proteins. Fasting plasma glucose (FPG), RPG and OGTT are based on serum glucose while hemoglobin A1C (A1C) is the most useful glycated protein in practice¹. FPG involves measurement of plasma glucose after overnight fast, being endorsed as test of choice by ADA. It's easy, inexpensive, and highly correlated with diabetic complications. The disadvantages include early morning appointments, requirement for fast, need to process the blood sample promptly (<2 hours after collection) and confirmation of results either at second occasion or with another test. RPG is easily obtained, does not require fasting, frequently employed as part of basic metabolic screen by most practicing physicians worldwide6. Downsides include prompt processing, additional office visit for confirmatory testing, lack of guidelines for interpretation of RPG levels obtained opportunistically and absence of direct comparison with diabetes-specific complications. OGTT is gold standard most sensitive diagnostic test of choice for diabetes and prediabetes avoiding overlooking of the patients with even mild disturbances in glucose metabolism7. However, OGTT is lengthy requiring committed nursing staff, has poor reproducibility and needs 8-hour fast. A1C has recently been endorsed by the ADA as a first-line test for both screening and diagnosis. Test can be performed independent of fasting status and provides an overview of glucose control overs months rather than a single point value⁸.

Many studies have shown that RPG can detect significant proportion of undiagnosed DM and prediabetes when combined with appropriate definitive diagnostic test like OGTT, FPG and A1C⁹. A study conducted by Friedman *et al*¹⁰, in 2013 revealed a frequency of 12.5% of DM when elevated screening RPG was followed with OGTT while another study conducted by Barasch *et al*¹¹, revealed frequency of 12.2% and 5.7% for DM

and prediabetes respectively when healthy individuals underwent screening RPG.

Limited work was done in Pakistan to identify potential value of RPG for diabetic screening. The primary objective was to determine utility of RPG to diagnose prediabetes and diabetes while secondary objective was to determine optimal cutoff value of IRG at which definitive diagnostic tests should be offered.

METHODOLOGY

This cross sectional study involved healthy individuals of both gender visiting AFIP/CMH Quetta for investigation of DM from Nov 2016 to Nov 2018. The study protocol was approved by the hospital ethical review Committee (Certificate no EXT-FC-CHP-04/READ-IRB/17/108). Non probability consecutive sampling technique utilized at outpatient department to enroll 280 patients (WHO calculator, confidence interval 95%, 5% margin of error and frequency 23.8%)¹¹. Non probability consecutive sampling was followed while patients with diabetes, pregnant, hospitalized, using concomitant medications such as chemotherapy, corticosteroids or immuno-suppressant and those unable to complete oral glucose tolerance test (OGTT) were excluded. A written informed consent obtained from all participants.

ADA guidelines were followed to stratify individuals as having NG, prediabetes or DM. IRG was defined as RPG between 5.6-11 mmol/l and all having IRG were subjected to confirmatory OGTT free of cost according to WHO guidelines. Samples were collected in properly labeled sample tube with NaF/EDTA by researcher themselves and transported to the processing room within half an hour. Glucose concentrations were measured within 2 hours of sample collection usingglucose hexokinase II method (ADVIA 1800® Siemens healthcare Diagnostics Inc., 511 Benedict Ave/Tarrytown, NY 10591, USA) following basic principles of photometry as per the manufacturer's instruc-tions and specifications. This kit has a sensitivity /lower limit of detection of 0.11 mmol/L, linearity up to 38.9 mmol/L, Intra-assay coefficient of variation (CV) 0.5% and inter-assay CV 1.3%. Frequency of NG, prediabetes and DM determined.

Statistical analysis was done using SPSS 24.0. Mean and standard deviation was determined for quantitative variables while qualitative data was reported as numbers and percentages and chisquare test and t-test used for inference statistics. Differences among the groups (NG, IGT and DM) were tested by one-way ANOVA. ROC curves were plotted and AUC was calculated. *p*-value ≤0.05 was considered statistically significant.

RESULTS

Among the 319 study participants recruited, 280 met the inclusion criteria and selected. Majority was female 156 (57.5%) vs 124 (44.3%) male.

(81.1%) individuals while 53 (18.9%) has impaired fasting glucose (IFG). Post glucose challenge analysis showed NG in 173 (61.8%), IGT in 69 (24.6%) while DM was found in 38 (13.6%) patients (table-I). Stratification of NG, IGT and DM with respect to age, gender and IRG performed revealed significantly more chances of IGT and DM if patient was >40 years, of female gender and had IRG >7 mmol/L at initial presentation (table-II). Frequency distribution revealed that 38 patients (13.6%) had diabetes, prediabetes being found in 69 (24.6%) of the total study subjects. Detailed analysis of various subcategories of IRG with respect to OGTT and FPG revealed significantly more diabetes and prediabetes if higher IRG and IFG were found at initial presentation

Table-I: Demographical variables of study participants (n=280)

Table-1: Demographical variables of study participants (n=280).					
Variable		Male	Female	<i>p</i> -value	
Age (years) (Mean \pm SD)		40.06 ± 11.08	39.25 ± 9.18		
Gender		124 (44.3%)	156 (57.5%)		
Impaired Random Glucose IRG (mmol/L)		7.12 ± 1.47	6.90 ± 1.17	0.157	
Fasting Plasma Glucose FPG (mmol/L) (n=280)					
Normoglycemia (227)	(81.07%)	104 (37.14%)	123 (43.93%)	<0.001	
Impaired Fasting Gluce	ose IFG (53) (18.93%)	53) (18.93%) 20 (7.14%) 33 (11.79%)		<0.001	
Oral Glucose Tolerance Test OGTT (mmol/L) (n=280)					
Normoglycemia (n=173) (61.8%)		83 (29.64%)	90 (32.14%)		
Prediabetes (69) (24.6%)		19 (6.79%)	50 (17.86%)	< 0.001	
Diabetes Mellitus DM (38) (13.6%)		22 (7.86%)	16 (5.71%)		
Table-II: Stratification of Normoglycemia, prediabetes and diabetes with respect to age, gender and impaired					
random glucose.					
Variable	Normoglycemia	Prediabetes	Diabetes Mellitus	<i>p</i> -value	
	173 (61.8%)	69 (24.6%)	38 (13.6%)		
$\Lambda \sigma (y_0 2r_0)$					

Variable	173 (61.8%)	69 (24.6%)	38 (13.6%)	<i>p</i> -value
Age (years)				
<40	128 (70.72%)	37 (20.44%)	16 (8.84%)	<0.001
>40	45 (45.45%)	32 (32.32%)	22 (22.23%)	
Gender		·		
Male	83 (66.94%)	19 (15.32%)	22 (17.74%)	0.003
Female	90 (57.69%)	50 (32.05%)	16 (10.26%)	
IRG (mmol/L)				
<7	155 (89.08%)	17 (9.77%)	02 (1.15%)	<0.001
>7	18 (16.98%)	52 (49.06%)	36 (33.96%)	

Mean age in male and female patients was 33.625 \pm 3.34 years vs 35.150 \pm 2.79 years with *p*-value 0.50 while mean IRG was 7.12 \pm 1.47 vs 6.90 \pm 1.17 mmol/L respectively with *p*-value 0.16 (statistically insignificant). FPG measurement preliminary to glucose challenge revealed NG in 227

(*p*<0.001) (table-III).

ANOVA was performed to compare the impact of IRG on likelihood of being normoglycemics, having prediabeticor diabetes. The differences in the variance between the groups were statistically significant as depicted by ANOVA F (2,300.80), p<0.001. The magnitude of difference in the means and the effect size was large (partial eta squared = 0.685). A Tukey post hoc analysis revealed that value of IRG was statistically significant different among normogly-cemics, patients withprediabetes and diabetes

Table-III: Detailed analysis of Impaired random glucose (IRG) sub categories with oral glucose tolerance test (OGTT) and fasting plasma glucose (n=280).

Category on OGTT	Impaired Random	Fasting Plasma Glucose		
(n=280) (100%)	Glucose IRG (mmol/L)	Normal	IFG*	<i>p</i> - value
Normoglyc	5.6-6	80	02	
	6.1-6.5	50	-	
emia	6.6-7	17	06	<.001
(173)	7.1-7.5	04	04	<.001
(61.8%)	7.6-8	05	-	
	> 8	02	03	
Prediabetes (69) (24.6%)	5.6-6	02	-	
	6.1-6.5	06	-	
	6.6-7	07	02	0.099
	7.1-7.5	12	08	0.099
	7.6-8	15	06	
	> 8	11	-	
Diabetes Mellitus DM (38) (13.6%)	5.6-6	-	-	
	6.1-6.5	-	-	
	6.6-7	-	02	0.086
	7.1-7.5	-	02	0.086
	7.6-8	06	02	
	> 8	10	16	

showed IRG as fair diagnostic test for prediabetes (AUC 0.771 [95% CI 0.717-0.825], *p*<0.001) having sensitivity 72.5% and specificity 77.3% (fig-2).



Figure-1: ROC curve showing the AUC of impaired random glucose for diabetes 38 (n=280) patients are positive for diabetes on OGTT).



Figure-2: ROC curve showing AUC of impaired random glucose for prediabetes (impaired glucose tolerance) 69 (n=280) patients are positive for impaired glucose tolerance on OGTT).

*Impaired fasting glucose

 Table-IV: Comparison impaired random glucose (IRG) in different groups based on oral glucose tolerance test (OGTT).

Variable	IRG (Mean ± SD mmol/L)	95% confidence interval	<i>p</i> -value
Normoglycemia (173) (61.8%)	6.25 ± 0.64	6.16-6.35	
Prediabetes (69) (24.6%)	7.58 ± 0.66	7.42-7.74	< 0.001
Diabetes mellitus (38) (13.6%)	9.35 ± 1.19	8.96-9.74	

(NG 6.25 \pm 0.64 CI = 6.16-6.35, IGT 7.58 \pm 0.66 CI = 7.42-7.74, DM 9.35 \pm 1.19 CI = 8.96-9.74) (*p*<0.001) (table-IV). Upon ROC curve application, optimal IRG cutoff value for diagnosis of DM was found 7.45 mmol/L (AUC 0.956 [95% CI 0.927-0.984], *p*<0.001, excellent diagnostic instrument) with sensitivity of 94.7% and specificity of 74.4% fig-1, however, same cutoff value

DISCUSSION

DM is metabolic chronic disease having very high prevalence of diagnosed and undiagnosed patients. ADA recommends early detection but prior efforts to screen for undiagnosed diabetes /prediabetes in population resulted in high expenditure as well as lowyield⁵. However, Gomez-Peralta *et al*¹², found that risk of undiagnosed diabetes in emergency department (ED) patients was 22.5% (95% CI 16.4-28.5%) and screening with RPG and A1C was promising in such settings. This prospective study utilized opportunity of value of RPG among individuals undergoing DM diagnostic workup.

The study population consisted of 280 patients. Mean age as well mean IRG was found comparable in both genders. OGTT performed showed NG in 173 (61.8%), prediabetes in 69 (24.6%) and diabetes in 38 (13.6%) patients. Significantly higher patients with diabetes and prediabetes were found if initial RPG and IFG were higher (p<0.001) suggesting significant correlation between levels of RPG and chances of having undiagnosed diabetes or prediabetes. IRG ≥7.45 mmol/L was found 94.7% sensitive and 74.4% specific to diagnose patients with diabetes, albeit with lower sensitivity & specificity for prediabetes tes.

Our results were in correlation with various studies carried out nationally as well as internationally¹³⁻¹⁵. Meek *et al*¹³, revealed that RPG \geq 7.5 mmol/l had 90% specificity and 70% sensitivity for diagnosis of diabetes in pregnant while Zimmer et al14, identified optimal RPG 6.95 mmol /1 (93% specificity, 40% sensitivity) and Ginde et al¹⁵. 6.67 mmol/l (89% specificity, 26% sensitivity) albeit with lower sensitivity but comparable specificity to our results. The frequency revealed by our study was higher than figures quoted by diabetes association of Pakistan (DAP) 3 but similar findings were presented by Bahijri et al16, for Saudi Arabia which may be due to selection bias. Akhtar et al, found prevalence of diabetes and prediabetes 9.27% & 11.43% respectively in a meta-analysis, prevalence of DM closely correlating with our study while that of prediabetes is lower. Similar figures are quoted by other studies conducted in various parts of Pakistan^{18,19,20}. Basit et al18,20, showed frequency of diabetes and prediabetes 26.3 & 14.4% which was higher as compared to our findings. A study conducted by Barasch et al¹¹, comprising subjects in 28 dental practices of National Institutes of Health (NIH) revealed frequency of 12.2% (51) for diabetes, 5.7% (24) for pre-diabetes when RPG was followed by definitive test. Majority patients were male (54.3% vs 45.7% females); the mean age was 52.2 \pm 14.7, sex ratio being comparable with our study while age being older.

Another study conducted by Charfen *et al*²¹, showed lower percentage of diabetes but higher for prediabetes when compared to our results. A RPG level \geq 140 mg/dl (7.78 mmol/l) triggered follow up testing at 06 weeks interval with OGTT. Twenty-seven (11%) were found to have diabetes, 141 (55%) had prediabetes, and 88 (34%) had normal results. All at-risk subjects with a RPG >155 mg/ dL (8.6 mmol/L) had either prediabetes or diabetes on follow-up testing. In our study, none of the patients having IRG <6.0 mmol /L was found to have diabetes while 26 patients out of 42 having IRG >8 mmol/L were diagnosed suffering from DM when underwent OGTT.

Silverman *et al*²², studied A1C as screening tool in acute care setting. Mean age was $49.7 \pm$ 14.9 years while on the basis of OGTT used a definitive test, the prevalence of previously undiagnosed prediabetes and diabetes was 31.9 and 10.5%, respectively.

This study found statistically significant difference of RPG value between groups (F148.88, p<0.001 ANOVA). Moreover, IRG cutoff value 7.45 mmol/L suggested for screening was found consistent with international literature.George et al 23 found that >50% patients presenting to the ED with undiagnosed diabetes having RPG >7 mmol/L fulfilled criteria for IGM. Ziemer *et al*¹⁴, found that 7 mmol/L has 93% specificity and 40% sensitivity for identifying diabetes when various RPG cut-offs were analyzed while Ginde *et al*¹⁵, recommended value ≥120-140 mg/dl which is quite close to our findings. Rhee *et al*⁶, suggested 93% sensitivity and 59% specificity of RPG >130 mg/dl strongly supporting our value.

Keeping in view morbidity and mortality of DM and vast availability of RPG even at primary care level, it may provide new avenues to diagnose and treat the disease at the budding and prevent myriad of complications.

LIMITATION OF STUDY

This study was carried out at two centers only leading to potential selection bias thus limiting generalizability of the results to population. Another limitation was lack of follow up and drop outs. Hence, these results must be interpreted with care. Moreover, determination of significant differences between groupsmay have been precluded by small sample size.

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Disclosure

This study was conducted at AFIP Rawalpindi/CMH Quetta after approval of synopsis from Research evaluation unit of College of Physicians and surgeons Pakistan and Ethical review board of AFIP / CMH Quetta.

Author Contribution

Mr. MTS had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

CONCLUSION

There was a considerably high frequency of diabetes and prediabetes among healthy individuals and RPG helps diagnose these. IRG ≥7.45 mmol/L was found optimal to initiate definitive testingto identify undiagnosed patients with diabetes and prediabetes.

It is certified that this original work is submitted with PAFMJ for publication and has not been submitted anywhere else as per protocols in vogue.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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