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Systematic Review

Pakistani Population under Dark Shadows Of Diabetes: Do we need a Different Protocol for Diagnosing Type-2 Diabetes Mellitus?

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ABSTRACT

Type-2 diabetes mellitus(T2DM) is taking on a mammoth toll in subcontinental population. Current international guidelines to screen T2DM requires although inclusive of majority of T2DM cases, still remain exclusive of many cases especially in Asian population. WHO data suggests Pakistan to be third in terms of diabetes cases and predicted to lead the world by next decade and half. Our country needs holistic, dedicated and evidence-based country-specific approach to manage this incoming sweetening menace of our times. Recent researches including Diabetes Prevalence Survey of Pakistan(DPS-PAK) and Pakistan Recommendation for optimal management of Diabetes from Primary to Tertiary Care Level(PROMPT) studies identifies an immediate need for timely focus for the Pakistani population. A wholesome multi-prong strategy for T2DM is needed. Our study group planned to review diabetes screening for our locale. While the obesity patterns and BMI have already been acknowledged as "different", we believe diagnostic screening age for T2DM to be varied for sub-continental population. We reviewed local and regional to trace down our normality definition for screening hyperglycemia. Any sensitive "medically defined stipulation for normality limit" for screening age mandates a well-researched evidence base with benefits likely to mitigate disease. Our reviewed data consistently highlighted an emerging trend among youth and adolescence for developing hyperglycemia among the Asians communities at an early age especially so in Pakistani population. Therefore, we suggested a very robust and early age (1-8 years with high incorporating high anthropometric indices) for screening T2DM for Pakistani population followed by periodic monitoring.

Keywords: Diagnostic cut-off, Hyperglycemia, Pakistani population, Type 2 diabetes mellitus (T2DM).

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INTRODUCTION

Pakistan is facing one the worst crisis of type-2 diabetes mellitus (T2DM) which is predicted to overtake the rest of the world in coming decade or decade and a half.[1] T2DM with multiple genetic and environmental triggers from food and sedentary lifestyle has impacted natural human equilibrium now favoring more glycemia. The time-lag from early life years exposure to pro-diabetogenic triggers to development of diabetes unfortunately remains fast-forwarded in developing economies especially so in sub-continental population. Whether the so termed "Starvation Genes" hypothesis, sedentary habits adopted over a small-time span, degree of consanguinity or possible unknowns, the pathology is taking the toll.[2] Though the estimates of diabetes differ among organizational measures, the International Diabetes Federation (IDF) has suggested total diabetes cases to be up to 26.7% in adults thus rightly earning the label of "Mother of All Diseases".[3] Pakistan is heading fast to champion the world in diabetes in next 10-15 years.

T2DM primarily considered a disease of adult age is now appearing early by adolescence in as young as 10 to 12 years of age with probable parental inheritance but also due to lifestyle of convenience and possibly other factors.[4] Whatever may be inside the puzzle box, diabetes in Pakistan is getting roots deepened by all every day in our community. We in third world country already suffering with diabetic macro and micro complications which not only sucks the juice from our struggling economy but also posing heavy workload to manage the multiple tailed complications. Some the recent high-quality studies raise from Pakistan need to be highlighted in this regard: PROMPT study by Shera *et al*., pointed out the various micro and macro vascular complications emerging within the country to suggest Risk Assessment of Pakistani Individuals for Diabetes (RAPID) scoring system to aggressively manage the disease.[5] The diabetes prevalence survey of Pakistan (DPS-PAK) assessed 18856 eligible participant in community level survey to identify the prevalence of

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prediabetes and diabetes as 10.91% and 16.98%. The interesting aspect of this study was the higher frequency of prediabetes to be 10.91% to diabetes i.e., 5.52% among population group of 20-30 years. This prevalence even increased to 25.74% for prediabetes and 16.01% for diabetes by next decade with further incremental rise by aging.[6] Second National Diabetes Survey of Pakistan (NDSP) from 2016 to 2017 using HbA1c after appropriate methodology dependent exclusions evaluated HbA1c values against gold standard Oral Glucose Tolerance Test (OGTT) among Pakistani population. While the study demonstrated some degree of discordance among diagnostic rates defined by OGTT and HbA1c, still the study identified 19.5% prediabetics and 11.9% newly diagnosed diabetics (NDD).[7] Important aspect to appreciate here was low mean of HbA1c i.e., 5.2(4.9-5.6%) among prediabetes and 6.2(5.3-6.8.4%). The study concluded a lower cut-off for diabetes in Pakistani population.[7] Alongside the NDSP 06 study also highlights rampant abdominal obesity figures between 82.1% in Baluchistan to 73.3% in Punjab further augmenting the notion of metabolic derangements going rogue in this part of the global community thus indirectly highlighting a worsening predisposition for metabolic disorders including T2DM.[8]

Regional data from "Bangladesh Demographic and Health Survey (BDHS)" survey highlighted similar trend with some preliminary guidelines. A study from Bangladesh by Chowdhury *et al*., highlighted a 35.7% prevalence in 2011, which hiked to 36.03% by year 2018 which seems like colossal rise.[9] Furthermore, the cost per diabetes as calculated by Islam *et al*., (Bangladesh) was 6.1:1 for a diabetes patient vs healthy individual. Pakistan with a 26.3% prevalence of diabetes can reduce our direct therapy associated spending for almost 60 Mn people suffering from this menace with probable billions of Pak Rupee saved in direct and indirect spending to manage T2DM.[10] However, the "National Family Health Survey" of India initiated screening between 15 to 29 years to identify 5.1% T2DM which increased to 13.2% and 25.2% between screening age gaps 30-44 year and 45-59 years. This practice in a country with almost 1.5 Bn people can thus be saved and almost 0.75Mn diabetics can be timely managed, an ambitious strategy but proactive in the times of a metabolic epidemic.[11] The Chinese data also suggest using an age defined cut-offs of 35 years for screening diabetes mellitus, which should preempt disease early to help 6.3 undiagnosed cases of T2DM early to institute early lifestyle interventions.[12] Thus, screening recommendations vary between our neighbors and WHO recommendations. However. I believe our population strata is genetically different along with social practices. This demands an aggressive and wholesome community-based approach to go ballistic to avoid championing in T2DM by next decade or early. Thus, our diagnostic targets, action measures and community level interventions must be accurate, precise and aggressive.

keeping in view the rising trends of T2DM in Pakistan, we plan to review the upper normality limit of hyperglycemia among our population and also intend to suggest diagnostic age for screening, age-wise differentiated glycemia cut-offs and time-gap between screening.

METHODOLOGY

We conducted a systematic review by incorporating related systematic reviews, randomized controlled trials, specific guidelines and quality observational studies among Asian countries and research dealing with Asians living in other European and North American countries. Our research team planned to initiate review process by first defining key research areas relating the theme along with critical questions divided between team members. The review process included literature from the last one decade as shown by key search queries as shown in Table-I. Search engines included PubMed and Google Scholar reviews on diabetes diagnosis within any Asian countries. Our review included a final total of 42 articles. We excluded articles published before 2019, where manuscript was not available in English language, articles where free full-text was not available or addressing any specified type of diabetes (Maturity onset of diabetes in Youth, autoimmune diabetes, Type-1 diabetes mellitus and other diabetes syndrome like DIDMOAD). We excluded duplicates, expert opinions, case studies and studies carried out on animals.

Table-I: Research Strategy Details Identifying Duration of Search, Key Search Words, Search Engines with Exclusion and Inclusion

Search term	N	Initial exclusions	Final exclusion / Duplicates	Finally considered
screening age for diabetes in Asians (PubMed)	647	550	76	21
screening age for diabetes in Asians (Google Scholars)	17200	17114	86	21
Total studies (N)	17847	17664	162	42

All selected Randomized Controlled Trials (RCTs), reviews and relevant guidelines were researched as per systematic review mandate, which included mandate of the study, study type with little details, assessment criteria and results. Short reference of author was also included. Detail of step-by-step review process have been described in detailed in PRISMA chart (Figure-1). We finally converge our selection to 42 manuscripts with several exclusions related to research mandate, availability of complete text, relevance to the theme, and selected outcome measures. Details of inclusions and exclusions are mentioned in Table-I and II. Disease wise specific exclusions were articles dealing with metabolic complications only, gestational diabetes, genetically defined diabetes sub types, Alzheimer' association with T2DM, T2DM with myocardial infarction, Maturity Onset Diabetes of Youth (MODY) and metabolic dyslipidemia in T2DM.

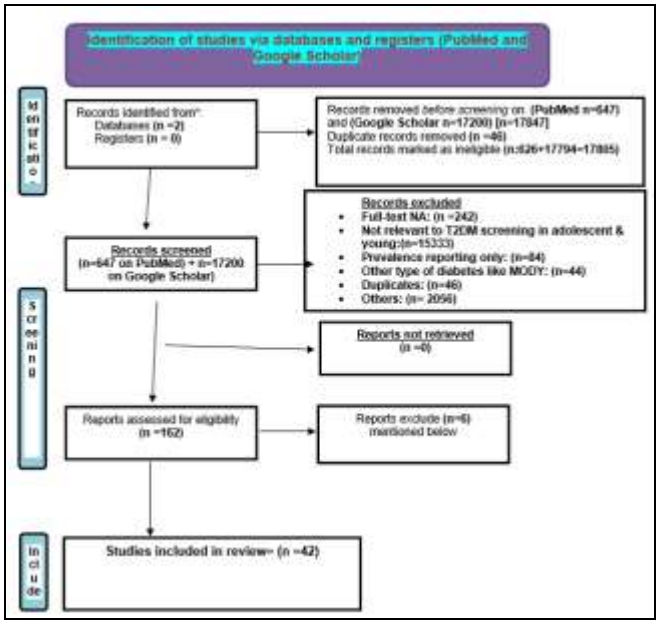

Figure-1: PRISMA Flow Diagram for Systematic Review

RESULTS

We incorporated PRISMA guidelines to extract relevant data selection, defining inclusions and exclusions as per and shared the details in Table-II. Based upon our research mandate and plan, we were finally able to incorporate 42 manuscript which especially dealt with our defined mandate i.e., screening age for diabetes in Asians. We utilized PRISMA Protocols to synthesize our findings which are shared in Table-II.

DISCUSSION

Our reviewed data consistently highlighted an emerging trend among youth and adolescence for developing hyperglycemia among the Asians communities at an early age especially so in Pakistani population.[5-7] As highlighted in discussion Pakistan stays at an asteroidal pace to champion the world in terms of T2DM prevalence.[4] Similar trends have been observed in neighbors. Emerging research with guideline endorsement are already available to suggest differential diagnostic approaches to deal with this in-rooted plague of our times. Alongside this skyrocketing prevalence of T2DM is rising with not only direct attributing to morbidity and mortality with much heavier financial toll indirectly burdening our planet's economy as IDF estimates now nearing 966 Bn USD (2021).[55] While cure still seems away we believe there is an unmet need for the Pakistani population to hold on brakes ASAP or else we are to land into a diabetes emergency which predisposed not only metabolic micro and macro off-targets but also allows an future viral/bacterial epidemic to hit hard to make happenings even worse.[9,11,12] We do also realize personalized and inter racial variations in size, BMI and disease susceptibility statistics which has been highlighted by various researchers. While ADA and certain other organizations have issued new guidelines on the subject, the rising concerns related to massive rise in T2DM among our younger population need a very proactive and data supported approach to define a population screening approach.[48, 55, 54]

Screening recommendations by researchers for screening T2DM subcontinental population including Pakistan differed markedly with most the Caucasian societies who either suggesting to maintain 40 or 45 years conventionally defined cut-offs.[14,16,40] However, some recent researchers have now been suggesting lowering glycemic cut-offs using (Fasting Plasma Glucose) by 35 years and few suggesting an extended range from 18-38 years.[17,21,24] Not many have included HbA1c to be redefined in the context of enhancing diagnostic sensitivity.[28,35,44,51,54] Once we segregate our reviewed article into groups as those negating/ inconclusive results for lowering screening age (n=3), only highlighting risk associated with late diabetes screening/sensitizers (n=12, recommending only early screening need (n=11) and then writeups directly defining a age specific lowered cut-offs (n=16), we feel confident enough to suggest a need for early screening to maximize reduction and early intervention of T2DM cases.

Table-II: Research Evidence for Screening in Diagnosing Type-2 Diabetes Mellitus (n=42)

Study mandate	Type of study	Assessment	Results (Screening recommendations)	Ref
R: Gender and age specified glucose cut-offs needed	Non-systematic review	Assessment of age & gender specified reference discussed	Gender & age -specific screening needed	Kautzky-Willer et al.13
SR: Assessing screening for T2DM implications	Cochrane Database Systematic Review using GRADE approach	92 full manuscripts to compare "Screening Group" (n=11,737) vs "No Screening Group" (n=4137)	Screening vs no screening for T2DM did not show significant differences	Peer et al.14
MA: Age impact on T2DM diagnosis	PROSPERO International Prospective Register of Systematic Reviews (CRD42016043593)	Age wise diagnosis of T2DM and association with diabetic complications	Early diagnosis of T2DM can reduce Mortality/morbidity	Nanayakkara et al.15
R: USPSTF-2022- Screening children/ adolescence for diabetes screening	Non-systematic review (Source: MEDLINE/ PubMed/Cochrane & trial registries)	Data reviewed for screening leading to therapy side effects for CVD, QoL and other side effects/harm	Reviewed data did not side towards harm or benefit of screening in children/ adolescence	Jonas et al.16
R: Early onset T2DM:Patients (aged:18-38 years) need optimized guidelines	Non-systematic review	Earlier age linked to increase morbidity and mortality	Screening early in life (18-38 year) can prevent and improve T2DM diagnosis and complications	Strati et al.17
RCT: Comparison of anti-diabetic combinations among young for glycemic improvements	SURPASS RCT: Programs comparing young-onset T2DM and late-onset T2DM for improvement in metabolic parameters via 3 interventions	SURPASS-1: Tirzepatide vs Semaglutide SURPASS-2: Tirzepatide vs Semaglutide +Metformin SURPASS-3: Tirzepatide vs Insulin Degludec	Young T2DM had showed more glycemia with little improvements metabolic health parameters	Zeitler et al.18
MA: Prevalence of T2DM &prediabetes in Malaysia	Prevalence study using GRADE recommendations	Systematic searched via Medline, Web of Science, Embase, & Google Scholar	-Prevalence as: Indians:(25%-35%), Malays (12%-19%), Chinese (9.8%-16%) -Early screening recommended	Akhtar et al.19
R: 12 countries from Middle East evaluated for T2DM prevention	Review study	PubMed, Web of Science, Google Scholar and EMBASE	Countries were encouraged to develop diabetes prevention plan including early screening	Haghravan et al.20
R: To Recommend Diabetes screening	Review study	Data reviewed for screening recommendation from ADA, WHO, USPSTF, AACE, RACGP &NICE	Screening recommended in all aged ≥35 years Adolescents: ≥19 years if obese	Lee et al.21
R: Literature reviewed from Philippines	Review study	Literature review on diabetes in Philippines.	Screening by using fasting blood sugar in healthy adults >40 years	Cando et al.22
Clinical Trial: 4 groups based upon % Body fat were compared for T2DM	Groups: (n=1128) Normal Weight Non-Obese=528 Normal Weight Obese=118 Overweight non-obese=63 Overweight obese=419	Normal Weight Obese demonstrated higher T2DM risk	Authors suggested %Body Fat measures to be included in clinical decisions	Xu et al.23
NR: Assess country wise incidence &prevalence of T2DM (2008-2019)	Narrative Review: Highlighting the need of region wise incidence and prevalence for T2DM	Highest prevalence was observed in China and USA while lowest in Denmark	Country-specific data T2DM varies Need for country-specific a-Diagnostic criteria b-Screening criteria	Lynch et al.24
R:(Feel4Diabetes) Community intervention to prevent T2DM (6 European countries)	Review: NCT02393872	-27 studies followed up ≥12 months -9 studies followed-up ≥6 months	Proactive research to preempt T2DM among vulnerable population group adolescent is needed	Kivelä et al.25
R: T2DM among non-Europeans appear early in life with usually lower cut-offs of BMI	Review article (Results from Genome Wide Association Study)	Certain genetic loci including CNQ1, ZRANB3, SLC16A11, and ZFAND3 remain population-specific	T2DM in Asian population is driven by specific, epigenetic leading to early onset of disease.	Yaghootkar et al.26
SR: Evaluating T2DM among 15-80 years in urban & rural areas oof India from 1994- 2018	Systematic review	T2DM prevalence was1.9% to 25.2%	There is a need for regular regional surveillance for T2DM	Atre et al.27
R: Diagnosis of pre-diabetes among Lebanese population	Expert panel consensus	Seven diabetes experts conducted a thorough literature search on diabetes and prediabetes cut-offs	-Screening age:45 years -Prediabetes: FPG: 100-125 mg/dl HbA1C: 5.7- 6.4%	Andari et al.28
R: Incidence of T2DM is increasing in young & young Chinese die 8 year earlier	Review article	Multiple metabolic risk including glycemia are contributing towards increasing morbidity and mortality	Increasing incidence of young-T2DM leading major complications and thus reducing human productivity Population-specific approaches are needed	Luk et al.29
Update: Changes in T2DM screening since 2008 Manage	American Diabetes Association (ADA) Guideline update	ADA recommendations increased to cover diabetes complications	No change in glucose age cut-off for screening at 45 years and then 3 yearly	Siegel et al.30
MA: Genetics (CF7L2 & CDKAL1) associated with early onset of T2DM in subcontinent	Meta-analysis	GWAS for age at T2DM diagnosis (n=34,001) i from 4 independent cohorts including European and South Asians	Asians in depict symptomatology of T2DM a decade earlier related to underlying genetics	Srinivasan et al.31
MA: Effect of urbanization on prediabetes and diabetes	Meta-Analysis from 48 studies	Gender-wise prevalence of T2DM in children living in rural and urban societies	Prevalence statistics in children as: -Males>females -Elder>Young -Urban>Rural	Han et al.32
R: T2DM incidence of in children & adolescents in US increased 4.8% since early 2000	Review	-	Screening to start around age 10 or at puberty especially if overweight or belonging to predisposed ethnic group	Rao et al.33
OA/CSA: US racial minorities screening thresholds for diabetes	NHANES (n=19335) on Asians, black and Americans) for age>35 years with equated BMI=25 kg/m2	Prevalence of diabetes from survey: Asian Americans:3.8% Black Americans:3.5% Hispanic Americans: 3.0% White Americans:1.4%	Screening should start early to include following considerations: Age 35 Ethnicity BMI	Aggarwal et al.34

R: T2DM incidence of in children & adolescents in US increased 4.8% since early 2000	Review	-	Screening to start around age 10 or at puberty especially if overweight or belonging to predisposed ethnic group	Rao et al.33
OA/CSA: US racial minorities screening thresholds for diabetes	NHANES (n=19335) on Asians, black and Americans) for age>35 years with equated BMI=25 kg/m2	Prevalence of diabetes from survey: Asian Americans:3.8% Black Americans:3.5% Hispanic Americans: 3.0% White Americans:1.4%	Screening should start early to include following considerations: Age 35 Ethnicity BMI	Aggarwal et al.34
OA/CSA: Defining optimal screening approach to identify prediabetes/ diabetes in youth	NHANES (n=14 119) from 10 -19 years from 1999-2016 as per ADA guidelines metabolic risk	25.5% of youth (10.6 million in 2016) were eligible for screening However, there were HbA1c seems to be a better screening modality to diagnose diabetes	1/4 were eligible for screening of diabetes. HbA1c is a specific and useful non-fasting test to identify high-risk youth	Wallace et al.35
OA: Comparison of Asians Indians with white Europeans for: -Age of onset -Obesity -Beta cell function -Insulin sensitivity.	(Comparative-cross sectional study): 3 x cohorts including: A. Asian Indians, the ICMR-INDIAB B.DMDSC c.White Europeans (ESDC) Age of onset, obesity, -Beta cell function	Young-onset diabetes up to 24-39% in Asians in comparison to Europeans having normal BMI i.e., 9.3% along with higher insulin resistance and related indices	Asians T2DM have: -Lean BMI -Have higher frequency of dysglycemia -Lower beta cell function -Have lower beta cell function.	Siddiqui et al.36
Rationale: Approximated 13% with age 18 or more have diabetes with 34.5% fulfilling criteria for prediabetes	Objective: To evaluate overweight with age (35-70 years) should have screening for diabetes?	USPSTF assessment suggest with moderate certainty about screening for diabetes	Clinicians should suggest potential T2DM subjects with prediabetes for screening/therapy	Davidson et al.37
Background: Differential BMI cut-offs among Asians need differential screening cut-offs for diagnosing T2DM	Cohort study: Electron health records may suggest: A->18 years without T2DM, B-Known ethnicity data and C-BMI (15-50) registered for follow up rom1990 "CALIBER phenotyping algorithm" was incorporated to identify incident T2DM	Findings: N=1 472 819 enrolled with multiple ethnic groups Median follow up: 6.5 years T2DM diagnosed= 97 823 (6 ·6%) South Asians had BMI cut-offs of 23.9 [95% CI:23 ·6-24], which were lowest among others including the Chinese and the Arabs	BMI cutoffs need revision for timely detection of T2DM among the South Asians	Caleyachett y et al.38
Aim: Measuring weight patterns with glycemia, BP, and lipids at diagnosis including of age of T2DM, age, gender and ethnicity	Methods: "UK Clinical Practice Research Datalink" [n=187,601] T2DM were included between 1998-2015 nd were compared with normal glycemic controls [n = 906,182]	Results: Younger age, South Asians and black early onset T2DM, increased T2DM and dyslipidemia	South Asians and black tend to develop T2DM almost a decade earlier	Wright et al.39
Review of evidence on T2DM screening to US Preventive Services Task Force (USPSTF) to evaluate mortality, morbidity, QoL and harms	Data sources: PubMed/ MEDLINE, Cochrane Library & Trial registries from 2019 to May 2021 Study	Inferences: (N=89 Reviews) -2 x RCTs, n= (25,120) participants found no significant difference between screening and control groups mortality at 10 years. -New T2DM: 5 RCTs (n=5138) from UKPDS improved with intensive glucose management. -Overweight T2DM: intensive glucose control using metformin showed improvement at 10-year	Outcomes: -No significant screening benefit -Insufficient data to prove better health outcomes -Harms of screening limited -Obese persons with prediabetes, interventions were associated with reduced incidence of diabetes	Jonas et al.40
The MASALA study: South-Asians in US have high T2DM risk	Longitudinal cohort study: Learning about key drivers relating atherosclerosis among South Asian Americans	Insulin resistance is high among the South Asians, and appears so at low BMI. Associations include: -Higher ectopic fat deposition -Early T2DM appearance -More and early atherosclerosis	Sout Asians are predisposed to early T2DM onset and atherosclerotic complications	Gujral et al.41 .
R: Assessing clinical criteria to manage T2DM CVD among Sout Asian population groups	Study background: South Asians are predisposed to early T2DM and CVD: Evaluating factors leading to higher morbidity and mortality	Findings: Factors leading to early T2DM and CVD In South Asians include: A-Adiponectin function B-Visceral adiposity Sedentary lifestyles D. Beta-cell dysfunction	Conclusion: Individuals from South Asians are predisposed to early-onset T2DM and CVD	Shariff et al.42
OBJECTIVE: To update trends in diagnosing diabetes in line with clinical practice by further validating diabetes diagnosis using confirmatory testing	METHODOLOGY: N=30,492 (aged: ≥20 years) An initial FPG >126 mg/dl needed confirmation by an HbA1c>6.5% Persistent undiagnosed DM was defined if either glucose or HbA1c was increased Study durations: -1988-1994 -2017-2020	RESULTS: -T2DM increased from 4.6% to 11.7% but undiagnosed T2DM prevalence persisted between 2-3% -Undiagnosed T2DM reduced from 33% to 18% -Undiagnosed diabetes was more prevalent, racial/ethnic minorities with missed diagnosis rates of rates from 23% to 61%	CONCLUSIONS: Diagnosed cases increased but non-diagnostic DM reduced. Ethnic minorities have high missed diagnosis rates	Fang et al.43
SR: Associating new prediabetes-related evidence with micro- & macrovascular complications	Research methods: -Search engines included MEDLINE, OVID, PubMed, and Cochrane 31/ 2020 (n=106 studies) -Outcomes included ACM, CVDM, stroke, CKD & retinopathy	Results: Prediabetes (FPG:100-125 mg/dl & HbA1c:6.0-6.4%) significantly associated with ACM, CVDM, CVD; CHD and stroke	Conclusion: Prediabetes is an elevated risk state for macrovascular and microvascular outcomes. The prevention and management of prediabetes should be considered.	Gujral et al.44
NR: Certain ethnic/racial and ethnic groups have high T2DM prevalence and incidence	Reviewed data: Higher complication rates in certain minority groups impacting direct and indirect care and cost	Recent Findings Provided improvement in diabetes care gaps exist between different ethnic minorities	Summary There is a requirement to improve care in Asian and other minority ethnic groups	Haw et al.45

SR&MA: T2DM Increase observed in diabetes / prediabetes	Methods: Search engines: PubMed & Scopus was for community-based studies describing prevalence of diabetes/pre-diabetes in urban/rural populations.	Results: Prevalence of T2DM increase over 5-decades as: 1972: 2.4-3.3% 2015-2019: 5.0-19.0%	Conclusion: Increasing trend in prediabetes & T2DM thus needing a robust proactive intervention	Ranasinghe et al.46
SR: Objective wa to measure T2DM global burden among age 15-39 years from 1990-2019	Data source: "Global burden of disease study-2019." Participants from 204 countries Main end-points for T2DM: -Age-standardized incidence rate -Age-standardized disability adjusted life years (DALY) rate -Age-standardized mortality rate	Results: From 1990 to 2019, increases are as: -Age-standardized incidence rate: 117.22 to 183.51 -Age-standardized disability adjusted life years (DALY) rate:106.34 to149.61 -Age-standardized mortality rate: From 0.74 to 0.78	Conclusions: Early age T2DM is increasing and thus T2DM complications Need to proactive approach to address adolescent or early onset T2DM	Xie et al.47
ADA-23 Guidelines: General recommendations for screening do not include any lowering of population-specific cut-offs or age	Specific recommendation special case oriented early screening (2.8 to 2.15)	-	Specific risk-based screening may be done at age-10 years or nearing adolescence age if BMI is > 85th percentile	Care D. 2. Classification and diagnosis of diabetes: standards of care in. Diabetes Care. 2023 Jan 1;46:S19.48
OR: Learning impact on patients having prediabetes once managed back to normoglycemia Chinese population	Methods: The current study included 14 231 Chinese (Average age:58 years) participants among senior Chinese citizen Study identifier: ChiCTRTNC-11001489.	Outcome measures included glycemia, overall CVD	Managing early onset hyperglycemia (prediabetes) can help various atherosclerotic cardiovascular complications was associated with a reduction in the future risk of CVD and all-cause mortality in a Chinese population.	Liu et al.49
NR: Depicting temporal trends in youth onset hyperglycemia and future implications	The epidemiology of early age (<20 years) hyperglycemia which may lead to early onset ACVD complications	Assessments: included -Prevalence among adolescence -Incidence among adolescence -Temporal trends -Projecting T2DM complications	Needs effective personalized preventive, anti-diabetic intervention and lifestyle management	Perng et al.50
Australasian Pediatric Endocrine Group guidelines	Targeted screening for children/adolescents with age > 10 years/puberty onset with BMI≥85 and < 95%) with >1 additional risk: -Mother with diabetes or GDM -Family history of T2DM in 1O relative -Race/ethnicity (South Asian, Middle Eastern, North African & Latino) -Insulin resistance signs like "Acanthosis nigricans", metabolic syndrome, dyslipidemia, hypertension, fatty liver, PCOS, SGA -Any use of psychotropic drugs Screening method: HbA1c/OGTT Screening frequency: 2–3 years/earlier if weight gain			Peña et al.51
Korean Diabetic Association (KDA):	Method: Lee et al performed one of the RCT on high-risk adults (n=1637) by using 75-gm OGTT test	Result: -17.2%: T2DM -59.3%: IFG (and/or IGT)	Screening recommendations: - Initiate from age 40 years in ALL -High risk/BMI>23: Screen from 30 years	Hur et al.52
T2DM in children and adolescents have higher reported prevalence in certain ethnic groups with slight aggressive clinical course toward complications	T2DM Children & adolescents can have early onset complications: -CKD -Other micro and macro-angiopathies	Ethnic variations in terms of age variation and development of complications between societies are quite prevalent	Age and gender optimized screening strategies need to be used for early and priority diagnosis	Bjornstad et al.53
Pediatric Endocrine Society, Endocrine Society, European Society of Endocrinology & ADA approves T2DM screening in high-risk children and adolescence	-Dx T2DM: HbA1c ≥6.5% on two different occasions -Dx prediabetes: HbA1c 6.0%- 6.4%on two different occasions -OGTT can also be incorporated for screening -A1c method needs to be standardized	-	An algorithm has been available for screening: Evaluation and Treatment of Prediabetes in Youth - The Journal of Pediatrics (jpeds.com). Accessed 24/Aug-2024.	Magge et al.54

R: Review, SR: Systematic Review, MA: Meta Analysis, NR: Narrative Review, CT: Clinical Trial, OR: Original research, CSA: Cross-sectional analysis

While the race differences in terms of genetics, color and size, so can be the biochemical parameters. Apart from the direct review generated evidence, the authors believe heterogeneity associated with normality definitions for various biochemical parameters and incident metabolic and non-metabolic factors including T2DM. There is evidence to the fact that HbA1c levels are higher in black but glycemic levels are lower.[56] Similarly, we have learnt that the Asian population in comparison to the Caucasians having similar BMI, accumulate more fat than the Caucasians thus leading them to develop early-onset

T2DM and other metabolic disorders.[57] Further support to our findings come in from genetic differences between different races which are the architect of our phenotype, metabolome and proteome including glycemic levels. Genetic studies utilizing a Genetic Risk Scores (GRS) based upon selective markers associates differently between ethnic group thus indirectly identifying variability in terms of complications between races.[58] We, therefore further augment the prevailing heterogeneity in within T2DM incidence and prevalence which may also be associated with underlying differential genetic architecture between population groups. Thus, possible diagnostic practice change after further study should identify age and population specific glucose ranges for our region. This effort should preempt any incoming metabolic disease like T2DM. Our review clearly highlighted the need for screening for T2DM among all Human's at an earlier certain age depending upon their demographics, ethnicity and race. We also believe these differences are important and allow us to define preclinical screening clinical decisions within the vast heterogeneity among Homo Sapiens. The suggested algorithm to screen T2DM is shown below. We believe T2DM is taking over faster than our expectations and soon our country will crossover mot statistical measures for depicting this disease. In Figure-2, we have depicted a screening protocol slightly stringent to manage T2DM aggressively.

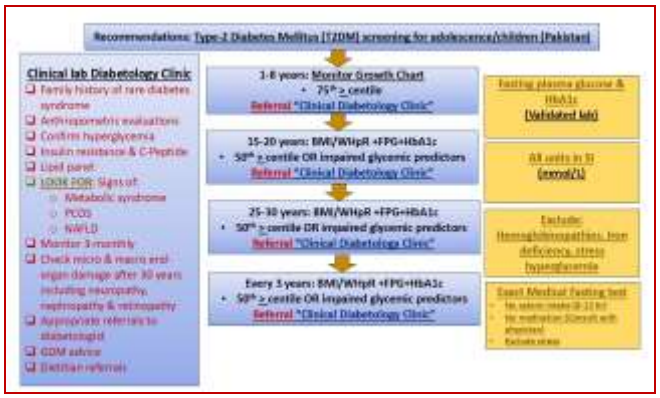

Figure-2: Overview of Screening Recommendations for Pakistani Population from Childhood to Adolescence and Onwards

We need to acknowledge few limitations associated with this write up: We believe T2DM was always considered as polygenic, probably combined effect of genetics at birth followed by myriads of epigenetic triggers. Genomic science is rapidly mining new ways to explore the disease and probably we may see T2DM classification. Thus, data can't be perfected due to ongoing exploration of the molecular pathogenesis. The guideline will soon need revision and upgradation. We used PubMed, Google Scholar and Cochrane reviews. We understand that multiple other search engines are there. Our review survey on pakmedinet.com with some relevant data which have cited but in general there was limitation in terms of quality evidence. Finally, we feel this study could not address diagnostic cut-offs for diagnosing T2DM due to limited Asian data, but still we tried to highlight that. We believe this could be separate area where both observational studies and control trials are needed.

Provided aforementioned limitations we believe this is one of the large-scale review on the subject from Pakistan especially once we consider the incoming menace of T2DM taking over Pakistan. We believe much more original and reviews are needed for exploring country's architecture of diabetes with aim to develop guidelines on diagnosing and managing T2DM. This reviewed data should also help allow future research avenue. We also suggest molecular studies on the subject, which could actually target the various genetic and epigenetic mutational targets and polymorphisms within our racial groups. Finally, diabetes must also be declared as of the mightier challenges for Pakistan and specific task force must be formulated to guide care pathway at primary, secondary and superlative research levels.

CONCLUSION

Our research identified an overwhelming need for screening children and adolescents at an early age. Keeping in view the Pakistani statistics on T2DM, we stay confident enough to suggest an aggressive approach to screen early (as schematic-I). All major labs must develop "Clinical Laboratory Diabetology Clinic" to accelerate optimized testing, exploring underlying phenotype to genotype match, research and should directly make referrals to Diabetologists and endocrinologists for therapy. We must adopt a very proactive approach to combat the incoming diabetes menace within our country.

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Authors Contribution

Following authors have made substantial contributions to the manuscript as under:

SHK & MQAK: Data acquisition, data analysis, drafting the manuscript, critical review, approval of the final version to be published.

AH & UM: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

MA & AA & EG: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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