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The National Jordanian Experts Consensus on Diagnosis and Treatment of Prediabetes

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Abstract: Background and aims: The prevalence of prediabetes is increasing in Jordan and the Middle East region, which is leading to increased risk of type 2 diabetes and micro- and macro-complications. The aims of the expert panel were to understand and evaluate the current prediabetes situation and practice in Jordan and make recommendations to standardize the management of patients with prediabetes in Jordan. Methods: A panel of diabetes experts met to discuss and review all the current literature related to the region and international guidelines on prediabetes. The panel evaluated and developed a comprehensive understanding, addressing the definition, screening, diagnosis, pharmacological treatment, and management of prediabetes with consideration of local factors. Results: The experts relied on international data to establish criteria with cut-off values for screening and diagnosis to identify asymptomatic patients with prediabetes and diabetes. The panel made protocol recommendations, including lifestyle modifications, and developed potential treatment algorithms to provide guidance on the overall management for Jordanian prediabetic patients. Conclusion: The panel of experts reached consensus recommendations with a tailored detection, screening, and treatment algorithm in anticipation for a country wide adoption and implementation. These recommendations would help increase awareness of prediabetes in Jordan and create local guidelines to better serve Jordanian physicians in the management of patients with prediabetes.

Keywords: Prediabetes, Consensus, Jordan, Management

1. Introduction

The number of adults with IGT (2019 estimates) is 374 million with almost half of them below 50 years old; this is due to the high prevalence of obesity in this age group [1, 2]. This number is also expected to increase to 548 million

adults between 20 and 79 years old by 2045, which represents 8.6% of the adult population [1]. These increasing numbers are associated with an increase in diabetes related morbidity and mortality worldwide [1]. IFG or IGT or raised glycated hemoglobin >5.5% (AACE), >5.7% (ADA) to <6.5% levels represent "Prediabetes" which is a stage of intermediate hyperglycemia. It usually occurs when a person's blood glucose level is higher than normal, but not high enough to be diagnosed with diabetes as defined by the 2018 Canadian Practice Guidelines [3], by the WHO [4] and the ADA [5].

Prediabetes increases the short-term risk of type 2 diabetes mellitus (T2DM) with a yearly conversion rate of 5 to 10% [6, 7]. Prediabetes is associated with an increased risk of retinopathy [8], nephropathy [9], heart failure [10], and coronary heart diseases [11]. Observational studies have shown that diabetes complications are linked to prediabetes [12]. Therefore, understanding prediabetes and managing it properly and timely, helps to decrease blood glucose levels and delay the progression to diabetes [13-15], thus reduces the global epidemic of T2DM [13]. It also reduces diabetes related cardiovascular and microvascular disease [16, 17].

The prevalence of prediabetes in MENA region is alarming [18]; 15.2% in Saudi Arabia [19], 14.4% in Kuwait [20], 14.7% in Bahrain [21], 7.0% in UAE [22], 29.1% in Iraq [23], 35.1% in Oman [24], 13.8% in Qatar [25], 9% in Yemen [26], 5.9% in Palestine [27], 8.6% in Syria [28], 5.1% in Lebanon [29], 5.9% in Tunisia [30], 8.6% in Libya [31] and 5.5% in Morocco [32]. In Jordan, according to the National Center for Diabetes, Endocrinology and Genetics JUST Study in 1995, the prevalence of IGT was 9.8% [33], 9.3% according to the Ministry of Health study in 1996 and 39.8% in 2007 [34], 13.4% in the 2004 National study and 25.4% in 1996 [34]. Thus, prediabetes is increasing at an alarming rate in Jordan.

Despite the high prevalence of prediabetes worldwide, in MENA region and in Jordan in addition to the risk of diabetes related complications, there are few recommendations regarding prediabetes diagnosis and treatment, and there are no approved licensed medications for the treatment of IFG and IGT in the Middle East. In addition, third party payers do not cover the costs of lifestyle changes for prediabetes and physicians have different opinions and approaches regarding its diagnosis and management. Moreover, there is an absence of defined targets for risk factors including glucose levels, weight, BP, and lipid levels [6].

2. Objectives

The main objective of the expert panel is to form a comprehensive understanding on the perspective of prediabetes definition, prevalence, diagnosis, management and the potential use of pharmacological agents in the management in Jordan.

3. Methodology

A panel of 10 diabetes experts (9 Jordanian and one international) met on the 24th of September 2018 to understand & evaluate the status of prediabetes diagnosis and treatment in Jordan and recommend its proper management protocol while taking into consideration the local factors. The experts conducted a comprehensive literature review search of databases such as Medline, EMBASE and Cochrane. The panel also reviewed websites of IDF, WHO, and the Ministry of Health of Jordan. Certain key terms were utilized to identify the relevant literature such as "prediabetes", "diabetes", "Middle East", "Jordan", "definition", "screening", "diagnosis", "treatment", "practice guidelines" and "complications".

4. Results

4.1. Definitions

"Prediabetes", "Non-Diabetic Hyperglycemia", "Diabetes stage 1" or "Early Stage of Diabetes"?

"Prediabetes" is defined as the transitional state that precedes the clinical onset of diabetes [35]. The IDF prefers the term "non-diabetic hyperglycemia" marked by an increase of blood glucose to a certain level below the diabetes range [4].

The ADA classifies prediabetes as an established risk factor for diabetes mellitus according to glycemic state of IGT and/or IFG and/or HbA1c [5].

In some cases the changes in glucose tolerance may be bidirectional, such as patients with T2DM who may revert to IGT status with weight loss [13], therefore "diabetes stage 1" or "early stage of diabetes" cannot be adopted. Thus, the expert panel agreed on the "Prediabetes" terminology.

What is the Prevalence of Prediabetes in Jordan?

According to the 8th edition of the IDF Diabetes Atlas, the national diabetes estimated prevalence in Jordan is 9.5% among people aged between 20 and 79 years old and the diabetes age adjusted comparative prevalence is 11.8%. These levels set Jordan as one the countries with a medium to high prevalence of diabetes [36]. The panel stated that this prevalence is outdated because it considers a population of 6 million while the population in Jordan is currently 10 million.

In the Middle East, there is a high prevalence of diabetes and it is expected to reach 72% by 2045 [37]. A study undertaken in Jordan, compared the mortality level in patients with diabetes and the number of deaths related to high blood glucose, showed that the prevalence of diabetes and related risk factors is 13.1%, obesity 28.1%, overweight 62.3% and physical inactivity 12.1% [38].

The DECODE study that evaluated prediabetes prevalence by age and sex showed an increase in the prediabetes prevalence in advanced age [39]. Furthermore, a cross-sectional study [40] showed that in 1821 students aged 18-25 years, the prediabetes prevalence was 18%.

A third study conducted in genetically isolated populations in Jordan showed that the prevalence of IFG was 18.5% for Circassians and 14.6% for Chechens, the prevalence of

diabetes was 9.6% for Circassians and 10.1% for Chechens [41]. The study also demonstrated that the prevalence of IFG and diabetes was significantly higher in men, older age groups, married, subjects of lower educational level, past smokers, and obese subjects. The low HDL-cholesterol was the most common abnormality in the two populations.

Therefore, the risk pattern for prediabetes in Jordan (risk factors, complications, risk of becoming prediabetic) is nearly similar to the one seen in other countries with little differences in prevalence.

4.2. Screening for Prediabetes

Development of prediabetes involves several factors such as genetics, insulin resistance, defects in insulin secretion, glucotoxicity, lipotoxicity, impaired incretin release, amylin accumulation, inflammation, oxidative stress and decrease beta-cell mass leading to beta-cell dysfunction [42]. Several groups have developed recommendations for prediabetes screening including the Canadian Practice Guidelines, the USPSTF and the ADA [3, 43, 44].

As per the Canadian Guidelines, prediabetes can occur silently; thus, it is crucial to repeat diagnostic testing if the person is known to have risk factors such as high BP, high levels of LDL-cholesterol, low levels of HDL-cholesterol and increased body weight and visceral fat [3].

According to the ADA, prediabetes is associated with obesity (abdominal or visceral obesity), dyslipidemia, high triglycerides and/or low HDL-Cholesterol, and HTN. Therefore, the ADA considers several criteria for both testing for diabetes and prediabetes (Table 1) [5].

Table 1. *Criteria for Testing for Diabetes or Prediabetes in Asymptomatic Adults[6].*

1. Testing should be considered in overweight or obese (BMI ≥25 kg/m^2 or ≥23 kg/m^2 in Asian Americans) adults who have one or more of the following risk factors:
a) First-degree relative with diabetes
b) High-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
c) History of CVD
d) HTN (≥140/90 mmHg or on therapy for hypertension)
e) HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L)
f) Women with PCOS
g) Physical inactivity
h) Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
2. Patients with prediabetes (A1C ≥5.7% [39 mmol/mol], IGT, or IFG) should be tested yearly.
3. Women who were diagnosed with GDM should have lifelong testing at least every 3 years.
4. For all other patients, testing should begin at age 45 years.
5. If results are normal, testing should be repeated at a minimum of 3-year intervals, with consideration of more frequent testing depending on initial results and risk status.

The USPSTF recommends screening for abnormal blood glucose as part of cardiovascular risk assessment in adults aged 40 to 70 years who are overweight or obese [43].

The IDF has also developed an online screening questionnaire evaluating the risk of having T2DM including 8 questions regarding the person's medical and family history. This test is based on the Finnish Diabetes Risk Score (FINDRISC) [45].

Due to high prevalence of obesity & other risk factors; The Jordanian experts panel recommendation for screening is summarized in table 2.

Table 2. *Jordanian Recommendation for Prediabetes Screening.*

No risk factors (repeat in 3 years)	>40 years old
≥ 1 risk factor	25 years old
BMI ≥ 25 kg/m^2	All age categories

The experts also recommend the Arabic validated/translated IDF questionnaire to be adopted.

4.3. Prediabetes Diagnostic Tests and FBG and HbA1c Cut off Values

Prediabetes is not yet regarded as an independent disease or disease stage but rather as a major risk factor for diabetes, micro and macrovascular complications. It is very important to realize that individuals with prediabetes when compared with normoglycemic subjects already have a "diabetic phenotype".

Thus, on top of hyperglycemia, these subjects usually have a higher BMI, waist circumference. Moreover, they are frequently dyslipidemic and have an elevated BP indicating that they have different components of the metabolic syndrome [46].

The diagnostic criteria for prediabetes have changed several times over the decades. The previous concept of non-diabetic hyperglycemia defined by the NDDG in 1979 was glucose intolerance mainly based on the OGTT; this was reviewed in 1997 by an international expert committee and endorsed by WHO in 1998 [46].

Various organizations, such as the WHO or the ADA have defined prediabetes with variable criteria. There are in fact, several types of blood tests and additional biomarkers that can be considered to determine if a person has prediabetes or not [42]. The WHO has used two parameters to define prediabetes: the IFG presented by the FPG of 110 to 125 mg/dL and the IGT presented by the 2-hr plasma glucose of 140-200 mg/dL after ingestion of 75 g of oral glucose load or a combination of the two based on a 2-hr OGTT [4].

The ADA has the same cut-off value for IGT (2-hr plasma glucose of 140-200 mg/dL) but has a lower cut-off value for IFG (FPG of 100-125 mg/dL) and has additional hemoglobin A1c based criteria > 5.7% to 6.4% for the diagnosis of prediabetes [5].

Prediabetes has been identified by mildly elevated glycated A1c. However, given the low sensitivity and /or

specificity to detect low/intermediary levels of dysglycemia that characterize prediabetes; it has been suggested to use this test in conjunction with a FPG or OGTT to enhance the diagnostic accuracy. As such, IFG and IGT remain the current recommendations for the identification and diagnosis of prediabetes [47].

The Canadian Practice Guidelines has also the same cut off value for IGT (2 hr plasma glucose of 140-200 mg/dL), as for IFG it has the same cut off value as the WHO (FPG of 110 to 125 mg/dL) and has as the ADA, A1c based criteria of a level of 5.7% to 6.4% for the diagnosis of prediabetes [3].

According to the IDF, levels of FBG between 100 to 125 mg/dL or 2-hour glucose following ingestion of 75-g glucose load levels between 140-199 mg/dL defines prediabetes. Increased levels of A1c in the non-diabetic interval can also be used to diagnose people at risk of T2DM [38].

In this regard, the panel agreed that the fasting blood glucose is more practical and easier to be applied and less costly than any other tests. Therefore, the FBG should be measured after a standardized fasting time of 8 hours, The Jordanian expert panel also suggested levels of A1c levels to be followed.

Table 3. *Jordanian Recommendation for Prediabetes Diagnostic Tests Cut-Offs.*

FBG	$\geq 100- \leq 125$ mg/dl
A1c	$\geq 5.7- \leq 6.4\%$ (ADA guidelines)
2 hours OGTT *	$\geq 140 - \leq 199$ mg/dl

*OGTT should be considered in certain cases.

4.4. Management of Prediabetes

Understanding prediabetes and managing it properly and timely, help in reducing the epidemic of T2DM [38]. The combination of physical activity and healthy weight management are two of the best management options to treat prediabetes according the AHA and the ADA. Lifestyle intervention in prediabetes should aim to reduce weight by 5% to 10% and maintain it for long periods of time. To achieve this objective, a program of regular moderate-intensity physical activity for 30-60 minutes daily is recommended at least 5 days/week along with a diet that includes caloric restriction, increased fiber intake, and (in some cases) carbohydrate intake limitations [6]. Many studies demonstrated the positive effects of lifestyle intervention during a period ranging from 2.8 to 6 years [13, 14, 48-51]. Even losing some weight for those who are overweight can have meaningful reductions in blood glucose.

By committing to and maintaining a healthy lifestyle (follow a healthy dietary pattern, lose body weight mainly from fats, increase physical activity, stop smoking and decrease stress), some people are able to reverse their prediabetes or avoid or postpone its progression to diabetes [48].

Medications such as biguanides, thiazolidinediones, α-glucosidase inhibitors, GLP-1 receptor agonists may be prescribed to manage prediabetes [7]. Other interventions such as anti-obesity drugs and bariatric surgery may also be needed [7].

The results of the Diabetes Prevention Program (DPP) Research Group showed that both metformin and intensive lifestyle intervention significantly reduced the risk of developing T2DM, by -31% and by -58%, respectively. It was also noted that lifestyle intervention is more effective in preventing diabetes as populations age and weight increases. After 10 years follow-up, the reduction in the risk of developing T2DM was -18% and -34%, respectively [48, 49].

Similar results were seen in the Finnish Diabetes Prevention study with a reduction of 58% in the incidence of diabetes over 4 years after diet intervention and the Da Qing Diabetes Prevention study (longest follow-up of 20 years) where the combined lifestyle intervention groups had a 51% lower incidence of diabetes in the first 6 years and a 43% lower incidence over the 20-year period [50]. A meta-analysis of US studies on body weight change showed a 71% weight regain after 4.5 years [52].

The DPP 10-Year Cost-Effectiveness results showed that lifestyle is cost-effective and metformin is marginally cost-saving versus placebo. Investment in lifestyle and metformin interventions for diabetes prevention in high-risk adults was considered as good value [49].

The expert panel recommendations are summarized in figure 1. Pharmacotherapy can be considered from day one in parallel with lifestyle management in certain cases.
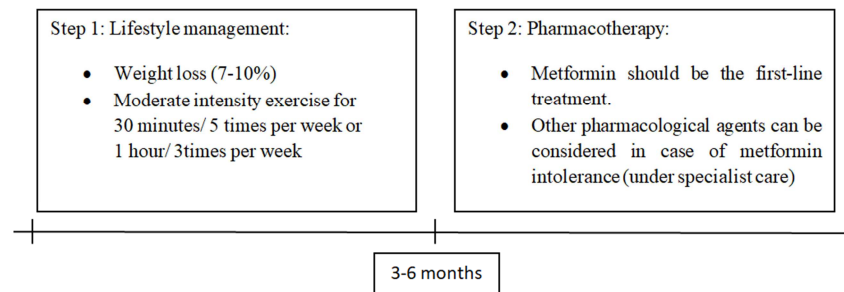

Figure 1. *Jordanian Recommendation for Prediabetes Management.*

Those above 50 years old should have a regular cardiac assessment before commencing on exercise.

Metabolic surgery (Bariatric surgery) is an option for morbidly obese patient with prediabetes.

4.5. Metformin Dosage in Prediabetes

In the DPP study, subjects were randomly assigned to 850 mg

metformin twice daily (n = 1,073) or placebo (n = 1,082) and followed up for 2.8 years. The results showed excellent adherence to metformin despite gastrointestinal side effects and a 31% decrease in the risk of developing diabetes. The optimal benefit was observed in patients with BMI 35 kg/m^2 - a 50% decrease in the risk of progressing to T2DM. A reduction of 1.7 kg was observed in the metformin group versus 0.3 kg weight gain in the placebo group. The weight reduction leading to improved insulin sensitivity and pancreatic function is viewed as a possible mechanism for reducing the risk of progressing to frank diabetes [16, 48, 49, 53].

Similarly, in the Canoe trial where metformin (500 mg) twice daily was combined with rosiglitazone (2 mg) in 103 patients, there was a beneficial effect in preventing the conversion of IGT subjects to type 2 diabetes [54].

The expert group concluded discussions on interventions to manage prediabetes as follows:

1) The therapy should be initiated with one tablet of metformin either 500 mg metformin immediate release or 500-750mg extended release once daily with the evening meal.

2) A stepwise increment of the metformin dose (5-7 days intervals) may improve gastro-intestinal tolerability. The recommended dose is 2000 mg standard release in divided doses with meals or 2000 mg XR once daily with the evening meal.

5. Conclusion

A literature review of the existing data on prediabetes, professional opinions and experience discussion between 10 diabetes experts resulted in a consensus on screening, detection, diagnosis and management of prediabetes in Jordan. The panel agreed that due to lack of local studies, Jordanian physicians should rely on international guidelines for cut-off values, mainly the ADA for prediabetes diagnosis. Moreover, subgroups with the metabolic syndrome should be identified and managed accordingly.

According to the Jordanian expert panel, FBG and A1c are the preferred tests for the diagnosis of prediabetes in Jordan and the cut off points that should be adopted are the following:

1. FBG for prediabetes diagnosis: 100 - 125 mg/dl as per the IDF guidelines
2. A1c: 5.7 - 6.4% as per the ADA guidelines

The Jordanian expert panel recommended that All people >45 years old without risk factors should be screened for prediabetes.

The expert group concluded discussions on pharmacological treatment for prediabetes management with metformin as the drug of choice in prediabetes management after failure of lifestyle management.

The expert panel agreed that more resources should be invested to properly manage prediabetes in Jordan.
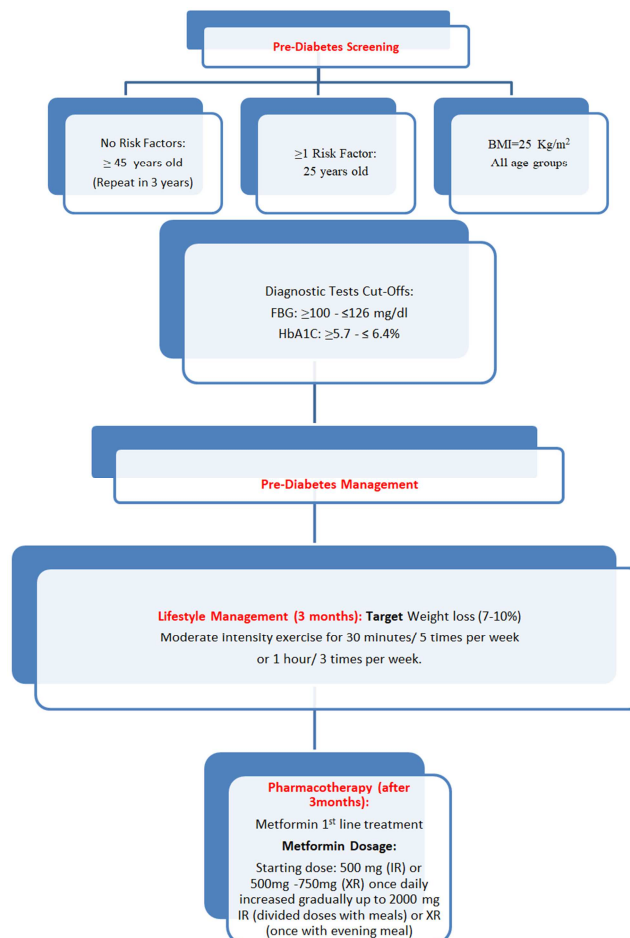

Figure 2. Jordanian Algorithm for Prediabetes Screening and Management.

Abbreviations

AACE	American Association of Clinical Endocrinologist
ADA	American Diabetes Association
AHA	American Heart Association
BMI	Body Mass Index
BP	Blood Pressure
CKD	Chronic Kidney Disease
CVD	Cardiovascular Disease
DECODE	Diabetes epidemiology: collaborative analysis of diagnostic criteria in Europe
DPP	Diabetes Prevention Program
FBG	Fasting Blood Glucose
FPG	Fasting Plasma Glucose
GDM	Gestational Diabetes Mellitus
GLP-1	Glucagon-Like Peptide-1
HTN	Hypertension
IDF	International Diabetes Federation
IFG	Impaired Fasting Glucose
IGT	Impaired Glucose Tolerance
MENA	Middle East and North Africa
NDDG	National Diabetes Data Group
NHS	National Health Security
OGTT	Oral Glucose Tolerance Test
PCOS	Polycystic Ovary Syndrome
T2DM	Type 2 Diabetes Mellitus
USD	United States Dollars
USPSTF	United States Preventive Services Task Force
WHO	World Health Organization

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