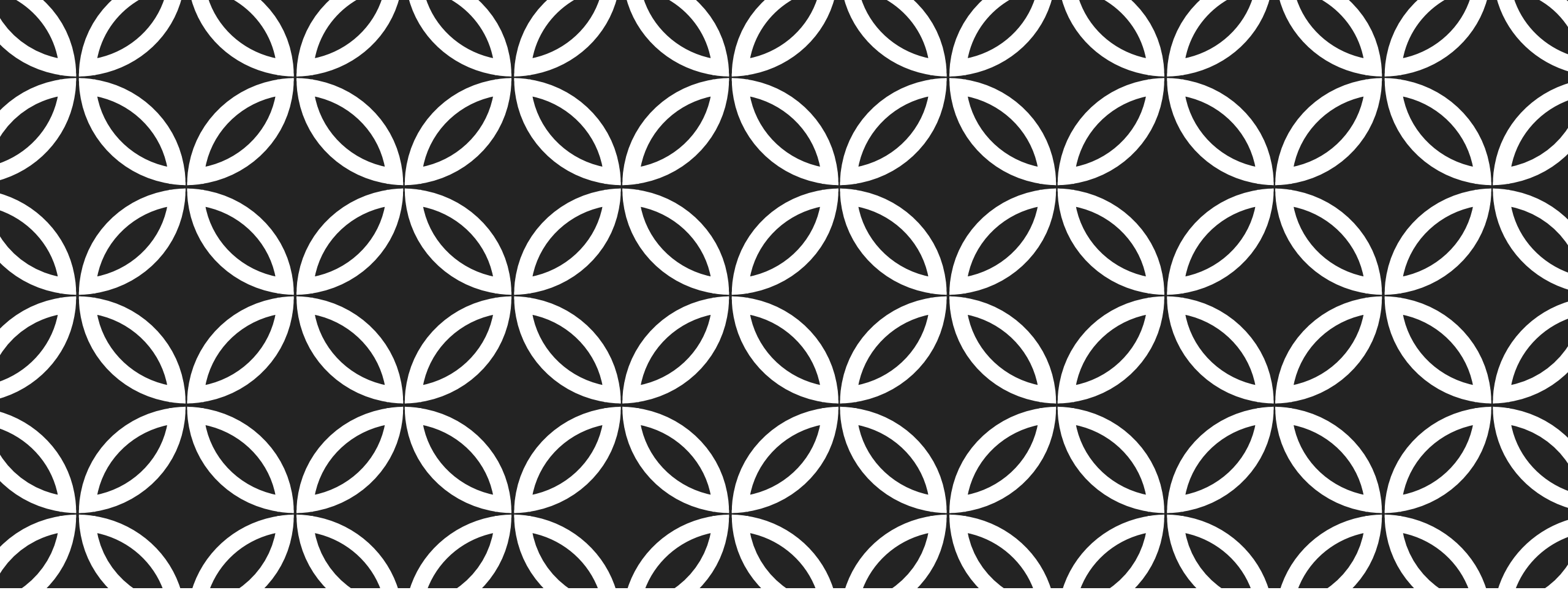

DIAGNOSIS AND MANAGEMENT OF PREDIABETES: A REVIEW

Presented by: Kiavash Semnani
Supervisor: Dr. Nasim Ebadati
Department of Family Medicine, TUMS, Ziaeian Hospital

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IMPORTANCE

- “Affects 720 million people worldwide”
- 10% progression to diabetes each year (US)

- Excess absolute risk during 6.6yrs:
  - Mortality: 7.36 per 10 000 person-years
  - Cardiovascular disease: 8.75 per 10 000 person-years

METHODS

- Pubmed, Cochrane database
  - English-language articles
  - January 1, 1990 - July 31, 2022
- Studies included (110)
  - Prospective cohort studies (58)
  - Randomized clinical trials (20)
  - Systematic reviews and meta-analyses (9)

METHODS

- Other sources
  - Practice guidelines (7)
  - National surveys (13)
  - Diagnosis studies (3)

DIAGNOSIS

Table 1. Diagnostic Criteria for Prediabetes

Criteria	American Diabetes Association (2023)	World Health Organization (2006)	International Expert Committee (2009)
Fasting plasma glucose, mg/dL	100-125	110-125	NA
2-h Postload plasma glucose (75-g oral glucose tolerance test), mg/dL	140-199	140-199	NA
Hemoglobin A_{1c}, %	5.7-6.4	NA	6.0-6.4

DIAGNOSIS

- HbA1c
  - Convenience: requires no fasting
  - Affected by:
    - Hemolytic anemia
    - Iron deficiency
    - Hemoglobinopathies
    - Pregnancy
    - Uremia
    - Race

SCREENING

- USPSTF:
  - 35-70yo, overweight or obese /3yrs
  - Annual monitoring for progression to diabetes
- ADA*: all adults older than 35yo /3yrs
- Low concordance between screening tests

Table 2.4—Criteria for screening for diabetes or prediabetes in asymptomatic adults

1. Testing should be considered in adults with overweight or obesity (BMI ≥25 kg/m^2 or ≥23 kg/m^2 in Asian American individuals) who have one or more of the following risk factors:
   - First-degree relative with diabetes
   - High-risk race and ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
   - History of cardiovascular disease
   - Hypertension (≥130/80 mmHg or on therapy for hypertension)
   - HDL cholesterol level <35 mg/dL (<0.9 mmol/L) and/or a triglyceride level >250 mg/dL (>2.8 mmol/L)
   - Individuals with polycystic ovary syndrome
   - Physical inactivity
   - Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
2. People with prediabetes (A1C ≥5.7% [≥39 mmol/mol], IGT, or IFG) should be tested yearly.
3. People who were diagnosed with GDM should have lifelong testing at least every 3 years.
4. For all other people, testing should begin at age 35 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.
6. People with HIV, exposure to high-risk medicines, history of pancreatitis

* ADA. Standards of Care in Diabetes - 2024

PATHOPHYSIOLOGY

- Impaired fasting glucose (IFG)
  - “Inappropriate” endogenous glucose production
  - Hepatic insulin resistance
  - Reduced hepatic glucose clearance
  - Decreased glucose uptake
  - Impaired beta cell function

PATHOPHYSIOLOGY

- Impaired glucose tolerance (IGT)
  - Skeletal muscle resistance
  - Delayed glucose uptake
  - Beta cell dysfunction (80%)
- Impaired HbA1c
  - Mean glucose level in past 2-3 months
  - IFG, IGT or both

EPIDEMIOLOGY

- Annual incidence: 6.2%, 11% with parental history
- Associated with increased body weight
- Simultaneous insulin resistance and beta cell dysfunction
- Postmortem studies: 40% decrease beta cell volume

EPIDEMIOLOGY

- Major risk factors:
  - Overweight or obesity (BMI $\geq$ 25): 80%
  - Older age (65yo or older)
  - Physical inactivity
  - Unhealthy diet
  - Genetic predisposition: OR 1.4 (1st degree family member, DM)*

EPIDEMIOLOGY

- Prevalence:
  - 38% US
  - 10.2% IGT, 5.7% IFG worldwide
- No effect for race
- Steady increase in the past 30yrs (US)
- IDF projection (2045): 11% IGT, 6.5% IFG

COMPLICATIONS

- Progression to diabetes
  - 5.8-18.3 /3yrs
  - 31% for IFG, 41% for IGT in 12yrs
  - 31% for HbA1c 5.7-6.4% in 10yrs
    - RR = 10 when 6.0-6.4%
  - 95.9% in 30yrs

COMPLICATIONS

- Progression to diabetes (CONT'D)
  - Lower rate among those older than 60yo
  - No significant ethnic differences

COMPLICATIONS

- Microvascular and macrovascular complications
  - More CVD risk factors and events
  - Increased all-cause mortality
  - Higher rates of hospitalization
  - Higher frequency of impaired cognition

COMPLICATIONS

- Microvascular and macrovascular complications
  - Retinopathy at baseline: 7.9%
  - Peripheral neuropathy: 7.5-16%
  - Chronic kidney disease: 9.7% (RR = 1.1-1.5)

❖ NO current recommendations for screening

SPONTANEOUS REMISSION

- Resolution in 1-5yr follow up: 33-59%
- Resolution in 6-11yr follow up: 17-42%
- Decrease with longer follow up

TREATMENT

- Meta-analysis of *47* trials (normoglycemia)
  - Strong evidence for lifestyle modification
  - Moderate evidence for pharmacotherapy

- Lifestyle adjustments: mainstay of treatment
- Pharmacotherapy: return with discontinuation

LIFESTYLE INTERVENTIONS

- Calorie restriction
- Increased physical activity
- Self-monitoring of food intake
- Physical exercise: 150min/week moderate-intensity

PROGNOSIS

- Achievement of normoglycemia
  - Lower baseline FBS, 2hPG
  - Younger age
  - Higher insulin response to glucose load
  - Weight loss
- Progression with normoglycemia
  - 2.6% vs 3.2% in 10yrs

Table 2. Efficacy of Lifestyle Intervention From Randomized Trials to Prevent Type 2 Diabetes

Source	Country	Study duration	Prediabetes definition	Age, y/BMI, mean (SD)	Study groups (No.)	Weight target	Mean follow-up, y	Intervention vs control		Reversal of prediabetes, %	Years of follow-up after active intervention
								Relative risk reduction for diabetes, %	Absolute risk reduction for diabetes		
Da Qing[32]	China	1986-1992	IGT	45 (9)/25.8 (3.8)	Diet (130) Exercise (141) Diet and exercise (126) Control (133)	No specific target	6	Diet, 31.5 Exercise, 46 Diet and exercise, 42	Cumulative incidence: 65.9% in control vs 47.1% in diet, 44.2% in exercise, and 44.6% in diet and exercise groups	NR	30
Finnish DPS[33]	Finland	1993-2001	IGT	55 (7)/31 (4.5)	Diet and exercise (265) Control (257)	>5% Weight loss	4	Diet and exercise, 58	Incidence rate per 1000 person-years: 32 cases in diet and exercise group vs 78 in control group	NR	13
DPP[34]	US	1996-2001	IGT (+ IFG in some)	51 (10.7)/34 (6.7)	Diet and exercise (1079) Metformin (1073) Control (1082)	7% Weight loss	2.8	Diet and exercise, 58 Metformin, 31	Incidence rate per 100 person-years: 10.8 in placebo vs 7.8 in metformin groups and 4.8 in lifestyle (diet and exercise) intervention groups	Lifestyle, 40 Metformin, 20	15
Japanese trial[59]	Japan	1984-2003	IGT (men only)	NR/24 (2.2)	Diet and exercise (102) Control (356)	No specific target	4	Diet and exercise, 67.4	Cumulative incidence: 9.3% in control group vs 3.0% in intervention group (diet and exercise)	Lifestyle, 53.8	NR
Indian DPP-1[35]	India	2003-2005	IGT	46 (5.7)/25.8 (3.5)	Diet and exercise (133) Metformin (133) Diet, exercise, and metformin (136) Control (136)	No specific target	3	Diet and exercise, 28.5 Metformin, 26.4 Diet, exercise, and metformin, 28.2	Cumulative incidence: 55.0% in control group vs 39.3% in diet and exercise, 40.5% in metformin, 39.5% in diet, exercise, and metformin groups	NR	NR
Indian DPP-2[60]	India	2003-2005	IGT	45 (6.2)/26 (3.3)	Diet and exercise (203) Diet, exercise, and pioglitazone (204)	No specific target	3	Diet, exercise, and pioglitazone (vs diet and exercise), 1.8	Cumulative incidence: 31.6% in diet and exercise group vs 29.8% in pioglitazone group	Lifestyle, 32.3 Pioglitazone, 40.9	NR

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); DPP, Diabetes Prevention Program; DPS, Finnish Diabetes Prevention Study; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NR, not reported.

TREATMENT

- No trial enrolled participants by HbA1c
- US DDP: IGT – lifestyle, metformin, placebo
  - Lifestyle:
    - 16 individual core sessions in 6 months
    - Twice monthly in-person maintenance sessions
    - Telephone contact between sessions
    - Higher report of musculoskeletal symptoms
  - Normoglycemia (3yrs): 40% lifestyle, 20% metformin / placebo

TREATMENT

- Effect of lifestyle modification mediated by weight loss*

  * Two trials without this finding: lower baseline BMI

- Effect persisted after discontinuation of intervention
  - US: 15yr cumulative incidence, 55% vs 62%
  - China: 30yr incidence, per 100 person-years, 7% vs 11.7%
  - Finland: 13yr incidence per 100 person-years, 4.5% vs 7.2%

TREATMENT

- No long-term effect on complications (DPP)
  - Same microvascular complications (15yr follow up)
  - Subclinical atherosclerosis (14yrs): 75% vs 84%
  - CV events (21yrs): 6.1 vs 5.3 /1000 person-years

TREATMENT

- Favorable long-term effects (Da Qing)
  - CV death (30yrs): 45.7% vs 56.3%
  - CV events (30yrs): 52.9% vs 66.5%
  - Microvascular complications: 25.1% vs 34.0%

Table 3. Randomized Clinical Trials of Medications for Prevention of Type 2 Diabetes

Source	Country/year of publication	Prediabetes phenotype	BMI at entry, mean (SD)	Study groups	Study size, No.	Mean follow-up, y	Relative risk reduction for intervention vs placebo (95% CI), %	Absolute risk reduction related to intervention
TRIPOD[78]	US/2002	IGT (women with a history of gestational diabetes)	30 (5.7)	Troglitazone vs placebo	266	2.5	55 (17 to 75)	Annual diabetes incidence rate: 12.1% in placebo group vs 5.4% in troglitazone group
STOP-NIDDM[79]	International/ 2002	IGT and IFG	31 (4.2)	Acarbose vs placebo	1429	3.3	25 (10 to 37)	Cumulative incidence: 42% in the placebo group vs 32% in the acarbose group
DPP[34]	US/2002	IGT and IFG	34 (6.7)	Metformin vs placebo	3234	2.8	31 (17 to 43)	Incidence rate per 100 person-years: 11.0 in the placebo group vs 7.8 in the metformin group
DPP[80]	US/2005	IGT	NR	Troglitazone vs placebo	585	0.9	75 (NR)	Incidence rate per 100 person-years: 3.0 in the troglitazone group vs 12.0 in the placebo group
XENDOS[81]	International/ 2006	Normal glucose regulation and IGT	37 (4.4)	Orlistat vs placebo	3305	4	37 (14 to 54)	Cumulative incidence: 9% in the placebo group vs 6.2% in the orlistat group
Indian DPP-1[35]	India/2006	IGT	25.8 (3.5)	Metformin vs placebo	531	2.5	26.4 (19.1 to 35.1)	Cumulative incidence: 55.0% in the placebo group vs 40.5% in the metformin group
Indian DPP-2[97]	India/2006	IGT	25.9 (3.3)	Pioglitazone vs placebo	407	3	2 (−44 to 33)	Cumulative incidence: 31.6% in the placebo group vs 29.8% in the pioglitazone group
DREAM[82]	International/ 2006	IGT and IFG	30.9 (5.6)	Rosiglitazone vs placebo	5269	3	62 (56 to 67)	Cumulative incidence: 25.0% in the placebo group vs 10.6% in the rosiglitazone group
DREAM[83]	International/ 2006	IGT and IFG	30.9 (5.6)	Ramipril vs placebo	5269	3	9 (−3 to 20)	Cumulative incidence: 19.5% in the placebo group vs 18.1% in the ramipril group

Voglibose trial[84]	Japan/2006	IGT	25.8 (3.8)	Voglibose vs placebo	1780	0.9	40 (18 to 57)	Cumulative incidence: 17% in the placebo group vs 8% in the voglibose group
NAVIGATOR[85]	International/ 2010	IGT and IFG	30.5 (5.4)	Nateglinide vs placebo	9306	5	−7 (−15 to 0)[a] (Favors placebo)	Cumulative incidence: 34% in the placebo group vs 34% in the nateglinide group
NAVIGATOR[86]	International/ 2010	IGT and IFG	30.5 (5.4)	Valsartan vs placebo	9306	5	14 (8 to 20)	Cumulative incidence: 36.8% in the placebo group vs 33.1% in the valsartan group
ACT NOW[87]	US/2010	IGT	33.7 (SE, 0.4)	Pioglitazone vs placebo	602	2.4	72 (51 to 84)	Incidence rate per 100 person-years: 7.6 in the placebo group vs 2.1 in the pioglitazone group
CANOE[88]	Canada/2010	IGT	31.7 (27.1-36.8)	Metformin and rosiglitazone vs placebo	207	3.9	66 (41 to 80)	Cumulative incidence: 39% in the placebo group vs 14% in the treatment group
SCALE[89,90]	International/ 2010	IGT and IFG	38.9 (6.4)	Liraglutide vs placebo	2254	3	79 (66 to 87)	Cumulative incidence: 6% in the placebo group vs 2% in the liraglutide group
ACE[91]	China and Hong Kong/ 2010	IGT	24.5 (3.1)	Acarbose vs placebo	6522	5	18 (6 to 29)	Incidence rate per 100 person-years: 3.8 in the placebo group vs 3.2 in the acarbose group

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); DPP, Diabetes Prevention Program; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NR, not reported.

[a] Denotes a lack of risk reduction.

PHARMACOTHERAPY (METFORMIN)

- No FDA approved medication
- ADA: metformin 850 bid
  - Younger than 60yo
  - BMI $\geq$ 35, FBS $\geq$ 110, HbA1c $\geq$ 6%
  - Prior gestational diabetes
- Higher GI symptoms: 77.8% vs 30.7%
- Monitoring for B12 malabsorption

PHARMACOTHERAPY (TZD)

- DDP (1yr): troglitazone 3% vs 12%
- DREAM (3yrs cumulative): rosiglitazone 10.6% vs 25%
- ACT NOW (3yrs): pioglitazone 2.1% vs 7.6%

PHARMACOTHERAPY

- α-glucosidase inhibitors
  - Acarbose
    - STOP-NIDDM* (3yr cumulative): 32% vs 42%
    - ACE (5yrs): 3.2% vs 3.8%
  - Voglibose (1yr): 8% vs 17%

* Decreased CV events: 2.2% vs 4.7%

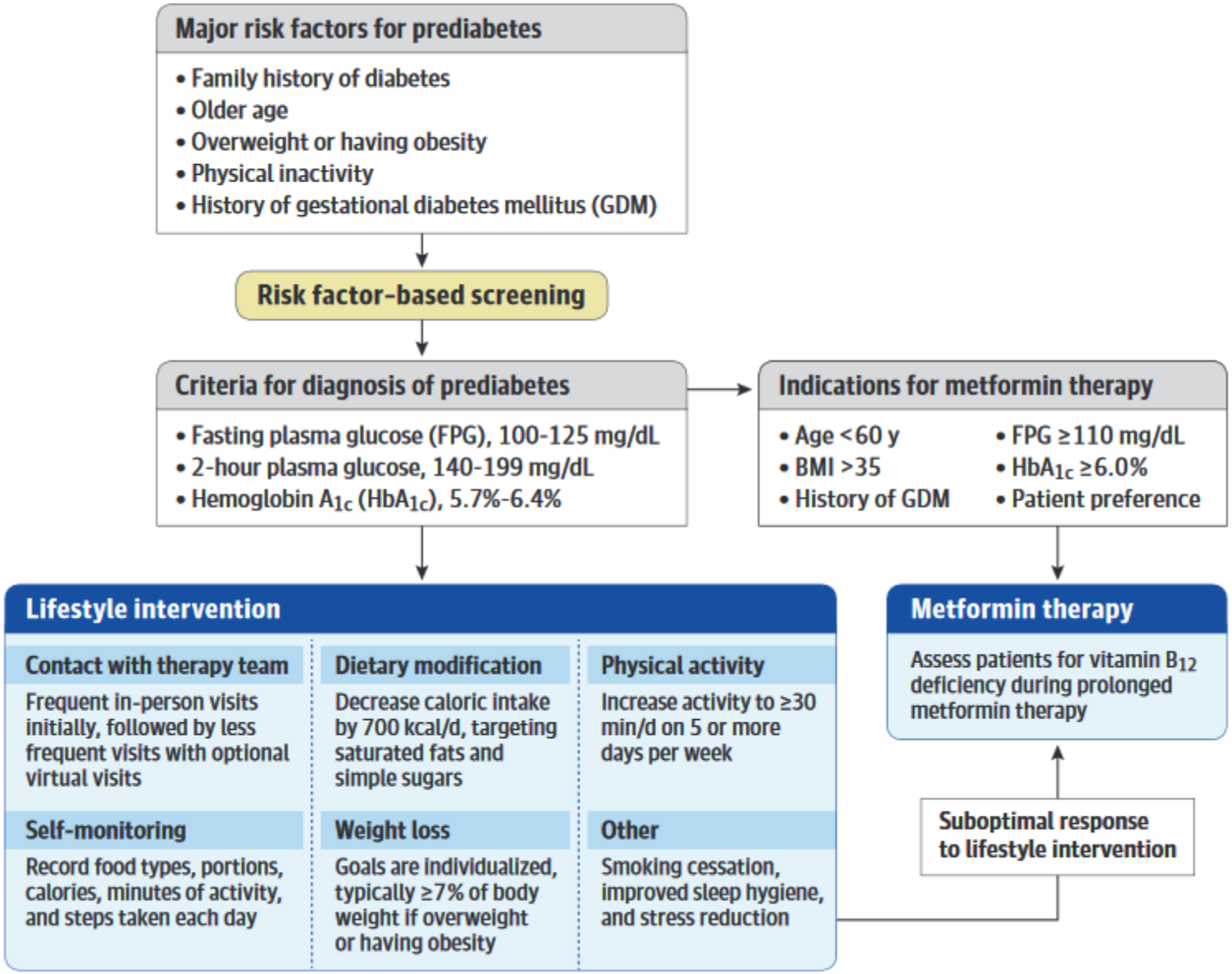
PHARMACOTHERAPY

- GLP-1 analogues
  - Liraglutide (3yr cumulative): 2% vs 6%
  - Semaglutide (68wks): 0.5% vs 3%
  - Tirzepatide: no data

PHARMACOTHERAPY

- Combinations
  - Metformin + lifestyle (3yrs): 39.5% vs 55%
  - Metformin + rosiglitazone (3.9yrs): 14% vs 39%

Figure. Approach to Screening, Diagnosis, and Management of Prediabetes



Lifestyle modification is the preferred initial approach after a diagnosis of prediabetes. BMI is calculated as weight in kilograms divided by height in meters squared. This specific algorithm has not been tested in randomized clinical trials.

LIMITATIONS

- No quality evaluation
- Limited search algorithm
- RCTs: variations in criteria
- RCTs: time without intervention