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PRE-DIABETES: DIAGNOSTIC CRITERIA AND THERAPEUTIC APPROACH

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Abstract

Pre-diabetes is defined as Impaired Fasting Glucose (IFG) or Impaired Glucose Tolerance (IGT) after a standard OGTT test. It is a high risk state not only because it may lead to diabetes, but also because of the associated complications such as vascular complications, nephropathy, and neuropathy that have been reported in people with Pre-diabetes. Pathophysiology of pre-diabetes state is linked to two main factors, insulin resistance and the relative deficiency of beta cells, these two mechanisms will eventually lead to abnormal glucose level. Pre-diabetes increases the risk of both microvascular and macrovascular complications. It is also an independent risk for stroke and cardiovascular disease. Early detection of pre-diabetes by screening can help in preventing vascular complications, and helps in changing the natural history of this disease by improving the islet cell function. Lifestyle modification like weight reduction and exercise reduces the risk of T2DM whereas pharmacological treatment with Metformin, Acarbose, Voglibose and Orlistat have all demonstrated significant reductions in progression to T2DM with very few adverse effects. In this review, we shall discuss and highlight the evidences that support the benefits of early intervention in Pre-diabetes and determine the cost effectiveness of lifestyle modification and drug treatment.

Key words

Pre-diabetes; Screening; Lifestyle modification; Pharmacological treatment.

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Introduction

Pre-diabetes is a state in which the blood glucose level is higher than normal, but lower than the diabetes threshold.

Pre-diabetes is defined by the American Diabetes Association (ADA) as the presence of Impaired Fasting Glucose (IFG) where fasting plasma glucose concentration 100 and 125 mg/dl, (≥5.6 - ≤6.9mmol/L) and/or Impaired Glucose Tolerance (IGT) which is an elevated 2 hours plasma glucose level >140 mg/dl but <200 mg/dl (>7.8 - <11.0 mmol/L) after a 75 g glucose load on the Oral Glucose Tolerance test (OGTT) and/or HbA1c value ≥5.7 - ≤6.4%[1].

The World Health Organization (WHO) defines IFG as Fasting Plasma glucose (FPG) >110 mg/dl and <126 mg/dl (>6.1 - <6.9 mmol/L) while it retains the same criteria for the diagnosis of IGT.

The American Association of Clinical Endocrinologists (AACE) guidelines do not support the use of HbA1c alone to diagnose Pre-diabetes. They consider that HbA1c value of 5.5 - 6.4% can be used as a screening tool, but the diagnosis must be confirmed by additional tests including FPG or OGTT[2].

Pre-diabetes is a high risk state not only because it may lead to diabetes, but also because of the associated complications such as vascular complications, nephropathy, and neuropathy that have been reported in people with Pre-diabetes. The AusDiab study showed that 21.7% of individuals with Pre-diabetes had at least one microvascular complication[3].

In this review, we shall discuss and highlight the evidences that support the early intervention and determine the cost effectiveness of lifestyle modification and drug treatment.

Search Strategy

Available studies and abstracts were identified through Pub Med and Medline data bases (From 2001-2016) and Cochrane data bases. Key search terms were prediabetes and diabetes prevention. All available studies and abstracts describing the relationship between early intervention and prediabetes were included. The reference list of review articles were also searched.

Discussion

Epidemiology and Prevalence of Pre-diabetes

T2DM prevalence increasing over the entire world. According to the International Diabetes Federation's (IDF) diabetes atlas, the number of patients with diabetes is expected to increase from an estimated 425 million in 2017 to 629 million in 2045[4]. In 2017 the number of people with IGT was estimated to be around 352 million people worldwide, amongstwhich 7.3% of were in the age group of 20-79 years. Recent increases are more remarkable in developing regions. By 2045 the number of people with IGT is projected to be around 587 million or 8.3 % of the adult population[4, 5]. Every year 5–10% of people with Pre-diabetes reach the clinical criteria for diabetes.

Rationale for the Definition of Pre-diabetes

In 1997 and 2003, The Expert Committee on Diagnosis and Classification of Diabetes Mellitus recognized an intermediate group of individuals whose glucose levels, although not meeting criteria for diabetes, are none the less too high to be considered normal[6,7]. These persons were defined as having Impaired Fasting Glucose (IFG) or Impaired Glucose Intolerance (IGT).

Individuals within these reference ranges (IFG or IGT) were referred to as pre-diabetes and were linked to relatively high risk of developing DM. It should also be emphasized that IFG or IGT should be viewed as clinical entities in their own right but rather risk factors for diabetes as well as Cardiovascular Disease (CVD). IGT and IFG have also been associated with obesity (Especially abdominal or visceral obesity) dyslipidemia with high triglycerides and/or low HDL cholesterol, and Hypertension.

In a systematic review of 44,203 individuals from 16 cohort studies with a follow –up interval averaging 5.6 years (Range 2.8-12 years) those with an $A1_C$ between 5.5 and 6.0% had a substantially increased risk of diabetes with 5 year incidences ranging from 9-25%. An $A1_C$ range of 6.0 to 6.5% had a 5 year risk of developing diabetes between 25 to 50% and relative risk 20 times higher compared with an A1C of 5.0%[8]. Another analysis suggests that an $A1_C$ of 5.7% is associated with diabetes risk similar to that of the high risk participants in the Diabetes Prevention Program (DPP).

Hence it is reasonable to consider an A1C range of 5.7 to 6.4% as in identifying individuals with high risk for future diabetes, a state that maybe referred to as pre-diabetes[9].

The Pathophysiology of Pre-diabetes

Pathophysiology of pre-diabetes state is linked to two main factors, insulin resistance and the relative deficiency of beta cells, these two mechanisms will eventually lead to abnormal glucose level[10]. Although both isolated IFG and isolated IGT individuals are due to insulin resistance, but the insulin resistance location is different. People with isolated IGT have normal to slightly reduced hepatic insulin sensitivity and moderate to severe muscle insulin resistance, while the individuals with isolated IFG have hepatic insulin resistance and normal muscle insulin sensitivity. Also there is a difference in the insulin secretion pattern between IFG and IGT. People with isolated IGT have deficit in the late phase of insulin secretory response to intravenous glucose, while the first phase remains normal[11]. On the other hand, there is a deficit in the first phase in individuals with isolated IFG.In addition to the above mentioned defects, in individuals with both IFG and IGT Glucagon-Like Peptide-1 (GLP-1) level is significantly decreased, compared to isolated IFG or IGT[12].

Screening for Prediabetes

Early detection of pre-diabetes by screening can help in preventing vascular complications, and helps in changing the natural history of this disease by improving the islet cell function[3].

Screening Criteria in Children (Adapted from ADA 2002)[13]

Both

- Overweight [defined as BMI>85th percentile for age and gender, weight to height ratio>85th percentile, or body weight>120% of ideal for height.

And two or more of the following risk factors:

- Family history of type 2 diabetes in 1st or 2nd degree relatives
- Race/ethnicity (Native North American, Hispanic American or Asian /pacific islander)
- Signs of insulin resistance (Acanthosis nigricans, hypertension, dyslipidemia, PCOS)

When and how to screen?

- Age of initiation: Age of 10 years or at onset of puberty, if puberty occurs at a younger age.
- Frequency: Every 2 years
- Test: FPS preferred

Screening of Asymptomatic Persons (ADA Recommendations)[14]

i) Screen beginning at 45 years of age, at least every 3 years

ii) Screen at any age and more frequently if the BMI is 25 or more and if the person has at least one additional risk factor:

- Family history of diabetes (First degree)
- High risk race (Black, Native American, Asian, Pacific Islander, Hispanic or ethnic group)
- HbA1c of 5.7% or more or IFG or IGT on previous testing
- History of gestational diabetes or delivery of baby weighing more than 9lb (4.1kg)
- PCOS
- Hypertension (BP≥140/90 mmhg or therapy for hypertension)
- HDL level less than 35mg/dl (0.91mmol/l) TG more than 250mg/dl (2.8mmol/l) or both
- History of cardiovascular disease
- Physical inactivity
- Other clinical conditions associated with insulin resistance (Severe obesity, acanthosis nigricans).

Use of validated risk calculator such as Finnish Diabetes Risk Score (FINDRISK) or Canadian Diabetes Risk Assessment Questionnaire (CANRISK) Framingham risk score. These risk calculators are used to select the patients for screening[15].

Method for screening includes (Random plasma glucose, FPG, HbA1c, OGTT or Glucose Challenge tests) depending on clinical and patient preferences[16].

Screening may lead to over diagnosis, unnecessary investigations, treatment and adverse effects, psychosocial and economic costs. There is lack of evidence to support screening subjects with low to moderate risk of diabetes. However with targeted approach for high risk patients, the screening costs could be reduced[15].

IFG or IGT: Which is a Better indicator of CV Risk?

The major disagreement in the classification of glucose homeostasis between the criteria issued by WHO and ADA focuses on whether diabetes should be diagnosed bymeans of a fasting or a 2-hPG. While different people are identified as diabetic and particularly as having IGH, when testing for fasting glucose than for a post-load glucose, itis clinically important to know how these two entities relate to mortality and the risk for CVD. Three early cohort studies, the White hall Study, the Paris Prospective Study, and the Helsinki Policemen Study, assessed the relationship between 2-hPG and the risk for CAD in European men. With known diabetes excluded, CVD mortality in individuals with a high 2-hPG in the White hall Study and in the Paris and Helsinki studies was twice that in subjects with normal glucose levels. In the Japanese Funagata Diabetes Study, survival analysis concluded that IGT, but not IFG was a risk factor for CVD.In a recent Finnish Study, IGT at baseline was an independent risk predictor of incident CVD and premature all-cause and cardiovascular mortality, a finding not confounded by the development of clinically diagnosed diabetes during follow-up.

The 23-year follow-up of the Honolulu Heart Programme suggested a dose–response relationship between 1h glucose after a 50g load and CAD mortality.The Chicago Heart Study of 12 000 men without a history of diabetes showed that white men with asymptomatic hyperglycemia had an increased risk of CVD mortality compared with men having a low post load glucose. The Rancho Bernardo Study indicated that elderly Californian women (But not men) with isolated post-challenge hyperglycemia [2-hPG≥11.1 mmol/L (200 mg/dL) and FPG <7.0 mmol/L(126 mg/dL)] had a significantly increased risk of CVD.

Several studies assessed the association of CVD with fasting and 2-hPG. Based on longitudinal studies in Mauritius, Fiji, and Nauru, Shaw et al reported that people with isolated post-challenge hyperglycemia doubled their CVD mortality compared with non-diabetic persons, whereas there was no significant increase in mortality related to isolated fasting hyperglycemia. In the Cardiovascular Health Study, including 4515 subjects above the age of 65 years, the relative risk for incident CAD was higher in individuals with abnormal glucose homeostasis (Comprising IGT, IFG, and newly diagnosed diabetes, detected by both fasting and 2-hPG) than in those with normal glucose levels. However, criteria based on FPG alone were less sensitive than the WHO 1999 criteria based on fasting and 2-hPG for predicting CAD.

A recent analysis of the US Second National Health and Nutrition Survey data, including 3092 adults aged 30–74 years, found a graded increase in mortality associated with abnormal glucose tolerance ranging from a 40% greater risk in adults with IGT to an 80% greater risk inadults with newly diagnosed diabetes.

The most convincing evidence for a relation between abnormal glucose tolerance and an increased CAD risk has been provided by the DECODE Study, jointly analyzing data from more than 10 prospective European cohort studies including more than 22 000 subjects. Death rates from all-causes, CVD, and CAD were higher in diabetic subjects diagnosed by 2-hPG than in those not meeting this criterion. Significantly increased mortality was also observed insubjects with IGT, whereas there was no difference in mortality between subjects with impaired and normal fasting glucose. Multivariate analyses showed that high 2-hPG predicted mortality from all-causes, CVD, and CAD, after adjustment for other major cardiovascular risk factors, but high fasting glucose alone did not. High 2-hPG was a predictor for death, independent of FPG, whereas increased mortality in people with elevated FPG largely related to the simultaneous elevation of the 2-hPG. On the other hand, FPG did not add any predictive information once 2-hPGwas entered into the model. All-cause and CVD mortality were increased in subjects with an FPG ≥7.0 mmol/L(126 mg/dL) but even among them it was a simultaneous elevation of 2-hPG that explained the increased mortality. The largest absolute number of excess CVD mortality was observed in subjects with IGT, especially those with normal FPG. The relation of 2-hPG with mortality was linear, but such a relation was not seen with FPG[17].

Complications of Pre-diabetes

Pre-diabetes increases the risk of microvascular and macrovascular complications

- Dutch TIA Trial Study Group: Showed that IGT is an independent risk factor for future stroke[18].
- Diabetes Epidemiology Collaborative Analysis of Diagnostic Criteria in Europe (DECODE): Showed that cardiovascular disease risk and all-cause mortality was increased with IGT, but there was less evidence for IFG[19]. Diabetic retinopathy is common in Pre-diabetes (About 8% of participants in the Diabetes Prevention Program)[19].
- Many studies showed increased prevalence of polyneuropathy mainly in isolated IGT compared with isolated IFG[20].
- Several reports show an increased prevalence of early diabetic nephropathy in terms of microalbuminuria in IGT patients, reaching 16% in comparison to only 4% of normoglycemic participants[21].

In conclusion, all complications of diabetes can occur in Pre-diabetes, and this is more obvious in IGT patients.

Diabetes Prevention

A. Life Style Modification

Obesity and sedentary lifestyle are established risk factors for T2DM[22]. Many clinical studies have shown that lifestyle modification including weight reduction and exercise reduces the risk of T2DM.

- **Diabetes Prevention Program (DPP) Research:** Randomized control trial involved 3234 individuals with Pre-diabetes from varied ethnic backgrounds, the intervention was exercise of about 150 minute/week together with weight reduction of > 7% during the period of the study. The development of T2DM was decreased successfully by 58% for IFG and IGT subjects with BMI > 24 kg/m^2, in compare with the control group[23]. The incidence rates for diabetes remained 34% lower in the lifestyle group after 10 year follow up for those participants, despite the weight regaining of about 5 kg in body weight[24].
- **Finnish Diabetes Prevention (DPS) Study:** This study showed a reduction in the cumulative incidence of T2DM by 58% for an observational period of 3.2 year, among IGT individuals, middle-aged, BMI > 25 kg/m^2, the participants performed moderate exercise (>30 minutes/day), they also lost >5% of their body weight by decreasing the amount of saturated fat and increasing the fibre intake in their diet[25]. 15% of risk reduction was achieved by lifestyle intervention during the period of 7 years follow up.
- **China Da Qing Diabetes Prevention Study (CDQDPS):** The participants with IGT were divided into 4 groups, one group for diet intervention alone, another group for exercise

intervention, one more group for both diet and exercise intervention, and finally the control group[26]. The incidence of T2DM was lower in three groups by about 45% compared with the control group for a 6 years observation period. After the active intervention in CDQDPS discontinued the prevention effect last up to 14 years[27].

- **Indian Diabetes Prevention Programme (IDPP-1):** The participants were IGT individuals all are native Indians, 28.5% reduction of T2DM incidences was observed over a 30 months period of follow up among lifestyle modification group (Life style modification advice only), while a higher progression rate from IGT to T2DM were recorded in the control group compared with the DPP, DPS and CDQDPS studies[28].

B. Pharmacological Treatment

When we evaluate the pharmacological intervention, the attention should be drawn to whether the medicine is really preventing the diabetes or rather masking it, this can be assessed by evaluating the incidence of diabetes after the wash out period of the drug from the body.

- **DPP Research:** Showed that Metformin 850 mg twice daily reduces the diabetes risk by 31% compared with the control group in prediabetes subjects[29].
- **IDDP Study of Indian with IGT:** 26.4% risk reduction was observed in the Metformin group. There was no significant synergistic benefit by combining metformin with lifestyle intervention[23].
- **STOP-NIDDM Trial:** 1419 IGT participants were allocated to control group and Acarbose treated group, 25% reduction of T2DM incidence were observed in the Acarbose group compared with the control group during a period of more than 3 year follow up[30]. And strikingly a large proportion of the IGT individuals returned to normal glucose tolerance by using acarbose[27].
- Another Alpha-glucosidase inhibitors, Voglibose was able to reduce the progression of T2DM by 40.5% for Japanese participants with IGT, compared with control group during a treatment period of about one year[31]. Although the high cost and gastrointestinal side effects make the use of Voglibose for prevention is controversial.
- **ACT NOW Study:** Showed that Pioglitazone 30 - 45 mg was effective in T2DM prevention during a period of about 30 month follow up period, also higher rate of participants with IGT returned to normal glucose tolerance by using Pioglitazone alone[32]. However, weight gain and fluid retention were common in the Pioglitazone.
- **XENDOS Study:** The participants of this study were obese, BMI > 30 kg/m^2 they received Orlistat for a period of 4 years. (Orlistat is a weight reduction agent that inhibits the activity of intestinal lipase in order to decreases the amount of triglycerides absorbed). The risk of developing diabetes reduced by 45% for IGT subjects, and 37.3% for all study participants compared with placebo group[33]. But the cost-effectiveness of this treatment has not been shown.

Incretin mimetics are considered to be potential drug therapies for individual with Pre-diabetes[34]. The impairment of GLP-1 response in T2DM and isolated IGT have been confirmed by many studies[35]. Unfortunately there is no randomised control trial targeting only isolated IGT or isolated IFG individuals to show the effectiveness of incretins for diabetes prevention benefits.

Nathan DM et al suggested that metformin should be the only drug considered[36]. Herman WH et al suggested that lifestyle modification was more effective than metformin in the DPP[37]. Knowler WC et al suggested that metformin was effective as lifestyle in participants with a BMI > 35 kg/m^2 [38].

Table I : Comparison of various studies using drugs for the prevention of onset of diabetes

STUDY	PATIENTS	INCLUSION CRITERIA	TREATMENT	REGRESSION TO NGT
ACT NOW (2001)	602	IGT	Pioglitazone 45mg OD vs Placebo	42% vs 28%
KAWAMORI (2009)	1780	IGT	Voglibose 0.2mg TID vs Placebo	67% vs 51%
DREAM (2006)	5269	IFG OR IGT	Rosiglitazone 8mg OD vs Placebo	39% vs 21%
ERIKSSON (2006)	33	IGT	Glipizide 2.5mg OD vs Placebo	56% vs 41%
HUNG (2005)	30	IGT	Rosiglitazone 4mg OD vs Placebo	33% vs 13%
BENNET (2004)	18	IGT	Rosiglitazone 4mg OD vs Placebo	44% vs 0%
FANG (2004)	124	IGT	Acarbose 25-50mg , Metformin 125-250mg vs Control	67% vs 52% vs 229%
DPP (2002)	2155	IFG OR IGT	Metformin 850 BID mg vs Placebo	21% vs 19%
STOP-NIDDM (2002)	1368	IGT	Acarbose 100 mg TID vs Placebo	35% vs 31%
LEHTOVIRTA	40	IGT	Metformin 250mg vs Placebo	40% vs 30%
LI (2001)	70	IGT	Metformin 250mg TID vs Placebo	85% vs 51%
WANG (2000)	60	IGT	Acarbose 50mg TID vs Control	80% vs 48%
ANTONUCCI (2000)	51	IGT	Troglitazone 400mg OD vs Placebo	80% vs 48%

Cost-Effectiveness of Pharmacological and Lifestyle Intervention

It is very important to look at the cost-effectiveness of the drug in addition to the benefits of preventive or therapeutic effectiveness, especially for long-term and wide applications of intervention programme. If we compare the other preventive or palliative intervention programme with lifestyle intervention, we found that lifestyle is much more cost-effective.

In Sweden they use a population-based simulation model sample which proved that lifestyle intervention programmes is saving an estimation cost of 1853 in 2003 per patient[39].

Accordingly, lifestyle modification will be a useful healthcare model in both developed countries and other developing countries.

Further Implications of Screening in Developing Countries

In developing countries, diabetes predominantly affects working-age persons, has high rates of complications and devastating economic impacts. These countries are ill-equipped to handle advanced stages of the disease. There are acceptable and relatively simple tools that can aid screening in these countries. Interventions shown to be cost-effective in preventing diabetes and its complications in developed countries can be used in screen-detected people of developing countries. However, effective implementation of these interventions remains a challenge, and the costs and benefits of diabetes screening in these settings are less well-known. Implementing screening policies in developing countries will require health systems strengthening, through creative funding and staff training.

For many compelling reasons, screening for hyperglycaemia preferably targeted, should be a policy priority in developing countries. This will help reorient health systems toward cost-saving prevention.

Conclusion

Life style modification including weight loss, exercise, and diet, slows the development of IGT to T2DM, this intervention is still the first choice for diabetes prevention. The beneficial impacts of such management seems to continue for years even after the original intervention.

Patients with IGT, IFG or both, or if HbA1c is 5.7 -6.4% he should be referred to an effective weight loss program targeting >7% of body weight, and increasing physical activity to at least 150 minutes/week.

Follow-up counselling seems to be very important factor for the success. At least annual monitoring for the development of T2DM is suggested in those with Pre-diabetes.

Pharmacological intervention using drugs with proven cost-effectiveness could be added to lifestyle modification. Metformin and -glucosidase inhibitors are suitable choices for initial pharmacological intervention for prevention of T2DM. Metformin is as effective as lifestyle especially for those with BMI > 35kg/m^2, age < 60 yrs., and women with prior GDM.

Implementation of the diabetes prevention strategies requires well organized systematic approach to detect pre-diabetes as early as possible, and provide the most appropriate intervention and follow up, in order to minimize the risk factor of diabetes and its complications.

Disclosure

The author declared no competing interests.

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