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Non-Pharmacological and Pharmacological Intervention of Type 2 Diabetes among Impaired Glucose Tolerance: A Systematic Review.

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Abstract : *The efficacy of various non-pharmacological and pharmacological interventions are to reduce the incidence of diabetes had been proven especially in the high-risk group such as those with impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT). The aim of this systematic review is to provide evidence on non-pharmacological and pharmacological interventions as supporting the early treatment for diabetes, and focusing on the pre-diabetic state in order to stop further deterioration of glycemic level in the predisposed subjects. There are convincing evidences that non-pharmacological and pharmacological interventions can lower the progression rate of overt diabetes and glucose status goes back to normal after a follow up of several years. Evaluations in many clinical trials were used the outcome measures such as weight reduction, and plasma blood glucose level. Based on the available evidences, there is the greatest hope and implementation of intervention programs in population at large, especially those of high risk for T2DM as an approach in preventing T2DM, even though the interventions into clinical setting is quite challenging and requires significant financial and human resources .*

Keywords : *Prevention T2DM, primary intervention, impaired glucose tolerance, pre diabetes.*

I. INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is a major public health problem and on increasing prevalence worldwide. To reduce the impact of T2DM, an action should be taken not only to treat the person with established diabetes mellitus but also to prevent the disease from occurring. T2DM is preceded by pre-diabetes for years before manifests as overt hyperglycemia. Pre-diabetes is also known for people who were diagnosed with impaired glucose tolerance (IGT) and/or impaired fasting glucose (IFG)[1]. This group has increased risk of developing T2DM[2] and cardiovascular disease[3-5]. The development of IGT / IFG is due to the defects in the action and/or secretion of insulin. The primary prevention of diabetes mellitus is based on knowledge of the natural history of the development of IGT and risk factors. It is an important to identify an intervention targeted on individuals who are at highest risk of developing the disease[6]. Two reviews[2,7] including fifth teen different populations from Europe, the United States of America, India, Africa and Pacific Island of Nauru reported an annual rate of developing diabetes in varied from 2 to 14 %. The risk was highest in those populations with the background of high prevalence of diabetes. Those with IFG had significantly increased a risk of mortality, which is related to cardiovascular disease.[8] Unwin and colleagues reported that IFG and IGT were strongly associated with CVD. IGT was strongly associated with CVD than IFG.[5] Every physician is looking for the efficient and effective interventions to prevent or delay the onset of diabetes mellitus. The type of interventions can be either pharmacological or non-pharmacological. The aim of this review is to establish the effective intervention in reducing the incidence of diabetes among people with pre-diabetes.

II. MATERIAL AND METHODS

Medline was searched via Pub Med, Google Scholar from 1970 to 2011 for randomized controlled trials (RCTs). A systematic review of the literatures was carried out to identify researches that focused on pharmacological or non-pharmacological interventions and to treat pre-diabetes as prevention of T2DM. The Medical Search Headings (MeSH) were used Type 2 Diabetes in Prevention, pre-diabetes, impaired glucose tolerance, and pharmacological or non-pharmacological interventions. Papers that focused on genetic, physiological and pathophysiological aspects will be excluded. All relevant titles and abstracts of the studies were reviewed.

Study selections: In order to ensure the inclusion of high-quality evidence, only RCTs were selected in this review. Studies need to involve the administration of non-pharmacological and pharmacological interventions in delaying or preventing T2DM. All participants were those who were diagnosed with IGT. The pharmacological intervention was used drugs for the treatment of T2DM. The common oral diabetic agents such as Biguanides, Sulfonyureas and Alpha-glucosidase inhibitors are available in the government clinics. The outcome measure

was the development of diabetes or oral glucose tolerance test (OGTT) monitoring. A total of 20 RCTs were selected in this systematic review.

III. RESULTS

3.1 Non Pharmacological Intervention

In this review a total of 12 RCTs were selected. The studies used non-pharmacological intervention i.e lifestyle modification to prevent T2DM (Table I). All participants have had IGT and T2DM as an outcome measure. The non-pharmacological intervention always been targeted at altering the behavioral factors such as obesity, dietary intake and physical activity. In Uppsala, Sweden, Cederholm[9] had identified 53 people with glucose intolerance and randomized them to a diet and physical activity regimen or no advice or therapy. The results after six months showed the intervention group was 2.2 times more likely to have normal glucose tolerance than controls. There were significant, though small, decreases in glucose area under the OGTT curve, systolic blood pressure, cholesterol and triglycerides compared to the controls. Limitation of information on diet and physical activity suggested that even with short term intervention with weight loss and modest increase in physical activity may help normalize the glucose tolerance. Pan and colleagues[10] in Da Qing China had identified 530 people and randomized them by using the primary care clinic. The intervention encouraged lower simple sugars and less alcohol consumption, more vegetable intakes and weight loss from BMI $\geq$ 25 kg/m^2 to $\leq$ 23 kg/m^2. Physical activity advice was aimed in increasing walking or running. Both interventions were conducted through individual and group sessions at a frequency, which weekly started and reduced to quarterly over the six year follow-up period. Compared to the control group who was given only limited written advice about diabetes and IGT. As a result, all the intervention groups had a significantly reduced incidence of diabetes over six years. This study gave a reasonable convincing data that lifestyle intervention can delay or prevent the diabetes.

A two-year randomized intervention conducted by Wing and colleagues[11] among overweight non diabetic subjects with family history of diabetes in which 72 of subjects had IGT at baseline. They were randomized to one of four interventions: control, diet, physical activity or both diet and physical activity. Throughout the period, total of participants dropped were only 27% in the last 18 months and weight regain occurred. The conclusion from this study was that, the three lifestyle approaches differed in the initial effectiveness but not in their long-term impact. However, the findings showed that modest weight loss in the entire group can reduce the incidence of diabetes is very important. The Finnish Diabetes Prevention Study[14,15] was intended the intervention could delay or prevent type 2 and worsening of cardiovascular risk factors among people with IGT. The intervention decreased 5% of body weight or more and also reduced saturated fat intake to less than 30% of energy consumed, while increasing dietary fiber and physical activity. The control group only received limited annual diet and physical activity advice. Result showed that the lifestyle intervention reduced the incidence of diabetes by 58%. This study also proved that modest weight loss was achieved through dietary changes and increasing the activity can result in substantial reduction in diabetes incidence. The Diabetes Prevention Program (DPP)[16,17] which involved 27 clinical centers and the participants were randomized into three intervention groups. The lifestyle intervention group was aimed to reduce body weight by 7% or more and increased moderate physical activity (usually brisk walking) to at least 150 minutes per week. The pharmacological group is discussed in the subsequent topic. Participants in lifestyle group lost an average of 5.6 kg of bodyweight compared to 0.1kg in the placebo group, and 74% met physical activity goal at the end of the core curriculum. The study concluded that the changes in dietary intake, increased activity and resulting weight loss will reduce of diabetes incidence even though the information to understand roles of the above changes on reduced diabetes incidence is not available. Most studies [12,13,18,19,20,21,22] have shown the benefits and impact of health and lifestyle changes in preventing the progression of IGT to T2DM.

3.2 Pharmacological Interventions Using Oral Anti-Diabetic Agent

Pharmacological interventions used hypoglycemic or anti-hyperglycemia agents. The rationale for drug intervention includes the following: 1) The drug may reverse one or more specific pathophysiological defects 2) Changes in lifestyle for healthy people are difficult to make even though they have demonstrated efficacy 3) Some other people are unable to change lifestyle due to disability or other diseases and it may be easier to take a drug over a longer period than take it significant behavioral change. Table II shows eight RCTs using pharmacological agent among impaired glucose tolerance specifically oral hypoglycemic or anti-diabetic agent. Papoz and colleagues conducted a randomized[22], double blind trial among those who had borderline glucose tolerance (by current criteria, diagnosed as IGT) and tested for glucose and insulin levels for every six months for two years. There were 28% drop-outs and at two years, there were no significant differences in glucose or insulin levels. However, the case of worsening to diabetes was not reported. Other studies[23,24] initiated with a small pilot study using Glicazide showed significantly reduction in fasting glucose, and this is led to The Fasting Hyperglycemia Study (FHS) at one year follow-up whereas the drug group showed significantly lower fasting

glucose and HbA1c but no changes in control group. After six years only 188 subjects remained in the analysis, and only 3.2% in the glicazide developed overt diabetes than in control group 10.8% (p=0.047, ARR 7.6/100 person-years). Li and colleagues used low dose Metformin (250 mg tid) compared to placebo among subjects with IGT and results suggested that 50% reduction in diabetes incidence occurred after one year follow-up. DPP as the first large randomized study also showed that metformin will delay or prevent diabetes in high risk IGT subjects. Unfortunately long term duration of the metformin effect is unknown. The STOP-NIDDM also adds in the list of pharmacological intervention that reduces the incidence of diabetes. The IDDP[19] was the second large trial, the 3 year cumulative incidence of diabetes was significantly reduced to similar levels in all interventions (control =55% vs LSM=39%, MET=40.5%) and no additional effect of combining lifestyle and Metformin (LSM+MET=39.5%). (10)

IV. TABLES

TABLE : Non Pharmacological Intervention – characteristics of studies included in review.

Study / Reference / Years	Study location / Number of subject (Male/Female) / Duration	Type of Intervention	Results
1)Cederholm, 1985[9]	Uppsala, Sweden N=53 with IGT, Aged 47-54 Follow-up 6 months	Diet + exercise (N = 25): lower sugar, fat, calories; at 6 months with abnormal OGTT given Glipizide (N=10/13- who did not normalized OGTT at 6 months) Control (N=18): no advice or therapy	Diet + exercise: RR=0.67, ARR=25.8/100 Person Year (PY) to remain glucose intolerant on OGTT at 6 months vs control. Decrease in glucose Area Under the Curve (AUCg), relative BMI, cholesterol, TGs and SBP (p<0.01) Glipizide: 4/10 became normal in additional 4-6 months; no control data.
2)Da Qing IGT and Diabetes Study. Pan et al, 1997[10]	China N=530 with IGT (283/247), All > 25 years, followed for 6 years.	Diet (N=130): lower fat, alcohol, higher vegetables, weight loss in those with BMI> 25 Exercise (N=141): increase by 1 unit/day (local scale) Diet + exercise(N=126) Control (N=133): information only	Diet: 10.0/1000 PY RR= 0.69 (p=0.028) ARR=5.7/1000 PY Exercise: 8.3/1000 PY RR=0.54(p=0.000) ARR=7.4/1000 PY Diet + exercise: 9.6/1000 PY RR= 0.58(p=0.001) ARR=6.1/1000 PY Control: 15/1000 PY RR=1.0 (8.1% dropout in 6 years)
3) Wing et al, 1998[11]	Pittsburgh, PA, USA 154 overweight non diabetic patients, Aged 40-55, Follow-up up to 2 years, 72/154 with IGT at baseline	Diet=D (N=37): lower fat, low calories Exercise=E (N=37): 1500 kcal per week moderate exercise Diet + exercise=D+E(N=40) combination of other interventions Control (N=40): written material	6 months: decreased in fasting glucose and insulin in D and D+E groups; also in lipids, BP 12 months: no change in fasting glucose between groups, although weight loss maintained in D, D+E at 60% and 72% of 6 months levels 24 months: Control 7% with Diabetes; D 30.3%; E 14%; D+E 15.6%, FPG, OGTT, weight loss not differ between groups
4) Wein et al, 1999[12]	Melbourne, Australia 200 women with prior GDM and IGT; aged 38 years; BMI=25; Follow-up 51 months	Intervention (N=100): 3 monthly dietician telephone contact; primarily healthy eating; brisk walk encouraged , not reinforced Control (N=100): baseline healthy eating, brisk walking, no reinforcement	Annual incidence rate: Intervention=6.1/100 PY Control=7.3/100 PY RR =0.83(95% CI 0.47-1.48, p=0.5) ARR=1.2/100 PY; 17% reduction
5) Lindahl et al, 1999[13]	Sweden N=186 (69/117) IGT Aged 30-60 BMI ≥ 27kg/m² Follow-up 1 year	Exercise and Diet: Weight reduction through a healthy, low energy, low fat diet. Participants were encouraged to increase their physical activity.	Significant reductions in body weight in the intervention compared with the control (-5.4kg vs -0.5kg) and also lower fasting glucose (-0.5mmol/L vs -0.3mmol/L, p=0.01) and improved parameters of fibrinolysis. Diabetes outcomes were not reported.
6)Erikson et al,1999[14] Tuomilehto, 2001[15]	Diabetes Prevention Study (DPS) Finland N=522 overweight with impaired glucose tolerance, 67% women (172/350), aged 40-60 years Follow-up 3.2 years	Intervention (N =265): diet, exercise, weight loss in 7 sessions in a year, then 4 x per year Control (N=257): annual information-limited advice on diet and exercise	Lifestyle intervention: incidence rate 3.2/100 PY Control: 7.8/100 PY Incident Diabetes 58 % reduction
7)Knowler et al,	Diabetes Prevention	Intensive lifestyle=ILS (N=1079): 16	ILS: incidence rate = 4.8/100 PY

2002[16] DPP Research Group, 2002[17]	Program (DPP) N=2161(680/1481) impaired glucose tolerance with elevated FPG ≥ 5.3 mmol/L, age ≥ 25 years, BMI ≥ 24kg/m² Follow-up 2.8 years	lesson curriculum on diet, activity, weight loss, participants individually encouraged to accumulate at least 150 min/week of moderate intensity exercise. Placebo (N=1082): annual meeting with written material on lifestyle	Placebo = 11.0/100 PY; 58% reduction in incidence; similar in genders, all ethnics group, all ages. ARR=6.2/100 PY
8) Liao, 2002[18]	USA, N= 70 Japanese Americans with impaired glucose tolerance, 55% female Follow-up 1.83 years	Intervention : Put on the American Heart Association step 2 diet plus 1 hour endurance exercise three time/week. Control: Less intensive step 1 diet and stretching exercises three times/week From 6 to 24 months, diet and activity were home-based and unsupervised.	58 completed 2 year follow up. Higher reversion to NGT among the intervention group (67% vs 30% in control group). Also significant sustained weight reduction seen in intervention group (-2.7kg at 6 months, -1.8kg at 24 months) than control (-0.9 at 6 months, +0.7 at 2 months)
9) Mersink et al, 2003[19]	Netherlands (Study on Lifestyle Intervention and Impaired Glucose Tolerance Maastricht-SLIM) N=114 (64/50) impaired glucose tolerance, aged ≥ 40, BMI ≥25kg/m² Follow-up up to 2 years	Exercise and diet: Participant were encouraged through goal setting to undertake 30 min of moderate intensity exercise per day.	88 completed for 2 years. Significant decreases in body weight (-2.3 kg) and 2hr glucose level (-1.4 mmol/L) between intervention and control. Greatest in those adherent to the combined diet and activity regimen.
10) Ramachandran et al, 2005[20]	Indian Diabetes Prevention Program (IDPP) N=531 with impaired glucose tolerance, aged average 46 years, follow up 3 years	Lifestyle modification(LSM) (N=133): diet + activity, monthly telephone, 6 monthly in person Metformin (MET) (N=133): 250 mg bid LSM + MET(N=129): Limited reinforcement	LSM cumulative 3 year incidence = 39.3% (Annual incidence rate (AIR)=16.6/100 PY; ARR=10.0/100 PY vs control 55.0% (AIR=26.6/100 PY) vs MET=40.5% (AIR=17.3/100 PY); ARR =9.3/100 PY) vs LSM + MET=39.5% (AIR=16.8/100 PY; ARR=9.9/100 PY)
11) Kosaka et al, 2005[21]	Tokyo Japan 488 Japanese males with impaired glucose tolerance, aged 30-70, Follow-up = 4 years	Intensive Lifestyle=ILS (N=102) visits every 2-3 months on diet, weight loss, increase activity Standard Intervention =STD (N=356) baseline session on weight loss or maintenance, smaller dietary portion size, reinforced every 6 months	ILS: 4 year cumulative incidence=3.0% (0.76/100 PY) vs STD= 9.3% (2.44/100 PY); 67% reduction in incidence; ACRR= 6.3/100 (ARR=1.68/100 PY); returned to normal glucose tolerance: ILS=53.8% vs STD=33.9%
12) Oldroyd et al, 2006[22]	Newcastle –upon-Tyne (N=78) impaired glucose tolerance, aged 24-75 years, follow-up 2 years,	Lifestyle Intervention (N=39): 12 routine visits with dietician and physiotherapists over 12 months on diet, physical activity. Participants were encouraged to undertake 20-30 min of aerobic activity 2-3 days /week. In addition, all participants were given a discount at local gyms. Control (N= 39): no intervention; 6,12,24 month assessments	Lifestyle: group 2 year cumulative incidence = 17.9% (9.9/100 PY) vs Control 20.5% (11.5/100 PY); ARR = 1.6/100 PY. Lifestyle lost 1.8kg vs 1.5 kg gain in controls. No change in mean blood glucose levels; significant improvement in whole body insulin sensitivity. No significant improvement in reversion to normal glucose tolerance among lifestyle group (20%) vs control (13%) at 24 month.

TABLE II: Pharmacological interventions – characteristics of studies included in review.

Study / Reference / Years	Study location / Number of subject (Male/Female) / Duration	Type of Intervention	Results
1) Papoz et al.1978[23]	France 120 men aged 25-55 years with borderline glucose tolerance; follow-up 2 years. Outcome: OGTT	Glibenclamide(G): N = 28 2 mg bid Biguanide(B) N=30 0.85 g bid G + B : N = 29 Placebo: N=33	Biguanide: no effect on glucose and insulin; significant weight loss Glibenclamide: no effect on glucose and insulin; less weight loss than in other three groups.
2) Page et al.	Pilot Study for	Glicazide 80 mg bid (N=6)	Glicazide: decreased fasting

1993[24]	Fasting Hyperglycaemia Study (FHS II) Abnormal fasting glucose, follow-up 6 months	Placebo (N=8)	glucose without change in insulin sensitivity but improved β cell function. Glucose level returned to normal after stopping drug Placebo: No changes in glucose or insulin levels. (short duration of follow-up, small number)
3) Karunakaran et al. 1997[25]	Fasting Hyperglycaemia Study (FHS II) – UK and France N=227 persons aged30-65; follow-up 1 year	Glicazide 80 mg bid (N=112) Control (N=115)	Glicazide: fasting glucose, HbA1c significantly lower, 2 h glucose and glucose area under the curve (AUCg) both higher, β-cell function improved slightly, no changes in insulin sensitivity, no change in % of diabetes. Control: Lower or no change of fasting glucose, HbA1c, 2 h glucose and AUCg in control group. No changes in insulin sensitivity, no change in % of diabetes.
4) Li et al. 1999[26]	Beijing, China N=90 with IGT, aged 30-60 years, follow up 1 year Outcome : OGTT, diabetes	Metformin: N=42 250 mg tid Placebo: N= 43	Metformin: 7.1% incidence of diabetes, RR = 0.51, p=0.50. Less IGT at follow up than placebo, fasting glucose, AUC glucose and AUC insulin, albumin excretion all lower at 1 year in efficacy analysis . slight weight loss(-1.4 BMI units) Placebo: 14% incidence of Diabetes Mellitus
5) DPP Research Group 2001[27]	Diabetes Preventive Program 27 centers in USA N= 2155 with impaired glucose tolerance, aged 51, BMI > 34kg/m^2 Follow up 2.8 years	Metformin 850 mg or Placebo twice/day. Annual meeting with written material on lifestyle	Metformin incidence rate=7.8/100 PY vs.placebo=11.0/100 PY: 31% reduction in incidence; ARR=3.2/100 PY: less effect in BMI <30; age >60 *NNT=13.9 to prevent one case
6) STOP-NIDDM 2002[28]	STOP-NIDDM 2002 Canada, Europe N=1368, with IGT, aged 40-70, BMI 25-40. Follow up 3.3 years	Acarbose 100mg tid (N=682) Or Placebo (N=686)	Acarbose 10.1/100 PY; HR=0.75 (95% CI 0.63 to0.90; ARR=9.1/100 PY. Higher reversion to normal glucose tolerance (p<0.0001). HR=0.64 (95% CI 0.498 to 0.813) using 2 positive OGTT as end point *NNT=11 persons with IGT to prevent one case
7) Ramachandran et al,2005[20]	Indian Diabetes Prevention Program (IDPP) N=531 with impaired glucose	Lifestyle modification(LSM) (N=133): diet + activity, monthly telephone, 6 mthly in person Metformin (MET)	LSM cumulative 3 year incidence = 39.3% (Annual incidence rate (AIR)=16.6/100 PY; ARR=10.0/100 PY vs Control = 55.0%

tolerance, aged average 46 years, follow up 3 years	(N=133):250 mg bid LSM + MET (N=129): Limited reinforcement	(AIR=26.6/100 PY) vs MET=40.5% (AIR=17.3/100 PY); ARR =9.3/100 PY) vs LSM + MET=39.5% (AIR=16.8/100 PY; ARR=9.9/100 PY)

V. CONCLUSION

Discussion: This review focused on the evidence of non-pharmacological and pharmacological agents in preventing T2DM. Interventions work in some societies may not work in others because social, economic, and cultural forces influence diet and exercise. This is a special concern in our country, where there is great regional and ethnic diversity in lifestyle pattern and where diabetes is especially frequent in certain ethnicity. Primary prevention play an important role, since this review showed that intervention can reduce the risk of T2DM among people with impaired glucose tolerance, and lifestyle interventions seemed to be at least as effective as pharmacological interventions. Known risk factors, obesity and physical inactivity are strongly linked with the increase in the prevalence and incidence of T2DM. This means that lifestyle interventions that aim to reduce obesity and increase physical activity help to directly address these risk factors. Thus, there is an urgent needs for effective public health strategies to combat the rapid expansion of the diabetic population. Both non-pharmacological and pharmacological interventions had significantly reduced the risk of developing T2DM in people with IGT. However, examining the best approach of intervention, either non-pharmacological or pharmacological depends on many issues such as potential side effects, life-long course of medication and compliance. Strategies will be needed to assist compliance before implementation for both interventions. The above evidences will help in re-orientating existing health system of Diabetes Prevention Program in health clinics. **CONCLUSION:** In order to curb the rising diabetes epidemic, the prevention of T2DM is an urgent priority. The prevention of diabetes is a major challenge to global public health. A clinical trial done among IGT showed that a reduction in the progression of IGT to T2DM can be achieved by lifestyle changes[9,10,11,12,13,14,15,16,17,18,19,20,21,22]. This intervention will be a real challenge to perform among high risk groups and populations. It is important to identify the high risk group such as IGT for diabetes prevention and to deliver lifestyle intervention. The use of pharmacological intervention such as Metformin and Acarbose can also prevent the progression of IGT to T2DM[19,22,23,24,25,26,27] All the above studies had found clearly support primary intervention for T2DM. No doubt all the clinical trials above showed that lifestyle modifications are considered the most effective means in delaying or preventing the development of T2DM. How to translate the finding of clinical research, into real world practice is a key issue to be addressed. The well trained staff are required in achieving the changing lifestyle among high risk group or participants in above studies/or this studies. We know that to achieve changes in lifestyle among those in high risk group or participants in above studies required strong efforts by well trained staff. Therefore, we need to carry out an effective lifestyle intervention program in a primary healthcare setting by using existing resources. It is better to do modest intervention that could produce beneficial effects on the incidence of T2DM over a period of time rather than vigorous intervention but only for

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