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Metformin versus Lifestyle Modification in Diabetes Prevention:

New Considerations in the Age of Healthcare Reform

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ABSTRACT

The *Affordable Care Act* will provide healthcare to 31 million previously uninsured Americans. Meanwhile, the country faces a growing diabetes epidemic. 25.8 million persons are diagnosed with diabetes. 33% of the US population is predicted to have prediabetes, which is a strong predictor of Type II diabetes. 174 billion dollars were spent in 2007 treating diabetes. If current trends continue, 1 in 3 are predicted to have diabetes by 2050. These figures are not sustainable. Exploration and implementation of new approaches to diabetes prevention is necessary. After searching common medical research databases, four randomized controlled trials were reviewed. Each article compared the use of Metformin vs lifestyle modifications, placebo or both in patients with prediabetes. The comprehensive review suggests lifestyle modifications are superior to Metformin as the preferred treatment in the presence of prediabetes. Though, Metformin was superior to placebo and should be considered in select patients. Earlier intervention to prevent diabetes in the age of healthcare reform is cost-effective, promotes sustainability and maintains patient quality of life.

DIABETES AND HEALTHCARE REFORM

The Centers for Disease Control (CDC) (2011) estimates that 25.8 million persons in the United States are currently affected by diabetes. It is estimated that 7 million of these persons are undiagnosed (p. 1). It is predicted that prediabetes, a strong risk for Type II Diabetes, affects 33% of the US adult population. Yet, only 10% of persons with prediabetes are aware of their diagnosis (CDC, 2012, p. 4). Despite the under-diagnosis of diabetes and prediabetes, rates of diabetes tripled from 1990-2010. In 2007 the direct and indirect costs of diabetes in the United States were estimated at \$174 billion (CDC, 2011, p. 7). Current trends predict that one of three adults will have diabetes by 2050 (CDC, 2012, p. 2).

The under-diagnosis of prediabetes and Type II Diabetes can be partially attributable to the high rate of Americans without health insurance. With imminent implementation of the *Affordable Care Act*, 31 million previously uninsured Americans will now have access to health insurance (Rosenbaum, 2011). Preventative services and screenings are hallmark traits of the care act and will be provided without copayment or deductible. (US Department of Health and Human Services, 2012). With screening comes the fundamental requirement that early detection of disease must lead to interventions proven to maintain health (UK National Screening Committee, 2011). As 31 million newly insured Americans begin to access healthcare services, there will be persons who will screen positive for prediabetes or diabetes that would have otherwise gone undetected. Rates for prediabetes and diabetes will rise, as will the costs required to treat these disease states. As we face the implications of healthcare reform, it is prudent to

explore and implement new cost-effective approaches to care. Early intervention to prevent diabetes must be emphasized, considering these seismic changes to the healthcare delivery system. The intent of this review is to determine if Metformin is superior to lifestyle modification or standard lifestyle for prevention of diabetes in persons meeting prediabetes criteria.

PREDIABETES

Garber et. al (2008) define prediabetes as persons with Impaired Fasting Glucose (IFG) of 100-125mg/dl and/or Impaired Glucose Tolerance (IGT) of 140-199mg/dl. IGT is correlated with decreased insulin sensitivity and is indicative of higher risk for Type II Diabetes; though IGT is less practical to carry out in a screening format (p. 936). Ngatena & Kapustin (2011) note research indicates prolonged hyperglycemic states can result in micro and macrovascular changes prior to the diagnosis of Type II Diabetes. These include cardiovascular disease, retinopathy, nephropathy and neuropathy (p. 552-553). Pancreatic beta-cell destruction begins in the presence of insulin resistance as a result of increased insulin secretion. As a result, up to 50% of beta-cell mass has become compromised at the time overt diabetes is diagnosed. At this extent beta-cell destruction is irreversible (Unger, 2007, p. 733). Progression of cardiovascular disease resulting from hyperglycemia begins prior to the diagnosis of Diabetes (p. 735). Therefore, it is becoming increasingly accepted that fasting glucose of 99mg/dl is the upper limit of normal (Garber et. al, 2008, p. 936).

Garbert et.al, (2008) state 6-10% of persons with IGT progress to overt diabetes annually. For those with combined IGT and IFG, the 6-year risk is potentially as high as 65% (p. 936). If glycemic goals can be achieved early in the progression of diabetes, beta-cell function can be preserved and risk for vascular complications become significantly reduced (Unger, 2007, p. 733). This warrants exploration of earlier interventions for prevention of Type II Diabetes and associated vascular manifestations of hyperglycemic states. A joint statement on behalf of the *American College of Endocrinology* (ACE) and the *American Association of Clinical Endocrinologists* (AACE) recommend screening for diabetes in patients with any one of the following:

- Family History of Diabetes
- Cardiovascular Disease
- Obesity/Overweight
- Sedentary Lifestyle
- Non-white ancestry
- History of IGT, OFT and/or Metabolic Syndrome
- Hypertension
- Dyslipidemia
- History of Gestational Diabetes
- Polycystic Ovarian Syndrome
- Active antipsychotic therapy by pharmacologic means (Garber et. al. 2008, p. 936-937).

Meanwhile, the *Agency for Healthcare Research and Quality* (AHRQ) (2008) recommends screening for Type 2 diabetes only in the presence of blood pressure greater than 135/80. AHRQ maintains “there is inadequate evidence that early diabetes control as a result of screening provides an incremental benefit for microvascular clinical outcomes compared with treatment after clinical diagnosis” (AHRQ, 2008). AHRQ states short and long-term harms of detection or early treatment is minimally significant.

METFORMIN

Edmunds and Mayhew (2009) state Metformin’s primary mechanism of action works by decreasing hepatic glucose production, thereby decreasing overall serum glucose levels. Decreased serum glucose levels prompt decreased insulin production from the pancreas causing less stress on beta cells. Metformin reduces HgbA1C levels by 0.9%-1.4%. Metformin does not potentiate hypoglycemia, rendering it a relatively safe medication (p. 573). It can only be used in renal competent individuals. Renal function is measured at the start of therapy and monitored as necessary. In rare circumstances, Metformin can induce lactic acidosis, which should be considered in patients with significant acute illness. Metformin should not be used in patients diagnosed with Congestive Heart Failure. Gastrointestinal side effects such as bloating, flatulence, and nausea are common when starting the medication but generally resolve in first 1-2 weeks of therapy (Edmunds & Mayhew, 2009, p. 578).

Consumer Reports (2011) note the monthly cost of generic Metformin averages \$7-\$24, which includes extended release formulations (p. 22-23). Metformin is approved by the Food and Drug Administration (FDA) for the treatment of Type II and is the most common first-line monotherapy. Micromedex (2012) notes Diabetes mellitus prophylaxis is not an FDA-labeled indication for use of Metformin. Other non-FDA labeled indications includes: Gestational Diabetes Prophylaxis, Polycystic Ovary Syndrome and Antipsychotic-pharmacotherapy induced weight gain (Micromedex, 2012).

LIFESTYLE MODIFICATION

Lifestyle modification in the presence of prediabetes has been directed towards reduction of serum glucose through adherence to improved diet. Improved insulin sensitivity occurs by skeletal muscle uptake of glucose through improved insulin transport of glucose. This occurs through weight loss and physical activity. As a result, Rosenzweig et.al (2008) recommend lifestyle modifications to include weight loss of 5-10% in the first year of therapy and routine physical activity of moderate intensity for at least 30 minutes, but preferably 45-60 minutes. This should be done at least 5 days of the week. Dietary recommendations include low fat, high fiber, unprocessed grains and the avoidance of foods with high glycemic index (p. 3673).

LITERATURE REVIEW

The literature review utilized common search engines such as CINAHL and Medline. Quantitative, randomized, control trials evaluating the use of Metformin in prediabetes were sought. Quality of studies was evaluated using the *Critical Appraisal Skills Programme* (2010) research appraisal tool. The following four articles were reviewed.

EFFECT OF METFORMIN ON PATIENTS WITH IMPAIRED GLUCOSE TOLERANCE

C.L. Li et al. (1999) randomized 90 subjects to either Metformin – 250mg three times daily or placebo in double-blind fashion. Subjects were drawn from a process that screened over 29,000 employees of an industrial corporation throughout Beijing, China. Inclusion criteria were those with IGT on two different occasions. Exclusion criteria included those who had been on metformin in the past or those with cardiac, renal or hepatic disease (p. 478). Patient education pertaining to diet, exercise, healthy lifestyle, diabetes knowledge, and symptom recognition were performed at visits on a three-month basis. The outcome measure was the incidence of diabetes after 12 months of therapy (Lin et al. 1999, p. 478).

Li et al. (1999) reported that 70 subjects remained in the study at the 12-month completion of the study. 20 subjects were lost primarily due to lack of pill compliance in both groups.

Of the 33 that remained in the metformin group, 28 (84.9%, $P=0.0001$) reverted to normal glucose tolerance. Fasting glucose decreased from the equivalence of 124.2mg/dl at start to 90mg/dl ($P=0.0001$). Glycosylated

hemoglobin decreased from 7.3 to 6.6 ($P=0.0001$). The metformin group also experienced significant decreases in serum insulin levels. One person (3.0% converted to frank diabetes (Lin et al., 1999, p. 479).

Of the 37 that remained in the placebo group, 19 (51.4%, $P=0.0001$) reverted to normal glucose tolerance. 6 patients (16.2%, $P=0.0001$) converted to type II diabetes. Fasting glucose decreased from 131.4mg/dl to 111.6mg/dl ($P=0.0001$). Glycosylated hemoglobin decreased minimally from 7.4 to 7.3 ($P=0.0001$). Overall there was an increase in serum insulin levels (p. 479). In summary, Li et. al's (1999) study suggests that Metformin is superior to placebo in the prevention of diabetes in persons with IGT. Though, there is evidence to suggest that basic diabetes education is beneficial given the decrease in fasting glucose in the placebo group.

This randomized, double-blinded control study is clearly defined with its intent, control and design. The population is clearly defined, but is limited to industrial workers in Beijing. Thus, cultural limitations apply when attempting to generalize to other populations. Age, sex and baseline measures are similar in both groups. A limitation is that fasting glucose in the placebo group is higher and could be considered overt diabetes. Confidence intervals for statistics are not provided, but P-values close to zero represent the data's strong statistical significance. Specifics of the education material and application into lifestyles would be helpful, given the decrease in fasting glucose in both groups. The quality of this study is also affected by the small sample size.

DIABETES PREVENTION PROGRAM RESEARCH GROUP

The most comprehensive study to date is conducted by the Diabetes Prevention Program (DPP). Knowler et.al (2002), as part of the DPP, conducted a randomized control trial of 3,234 participants from 27 healthcare centers that quantitatively evaluated the prevention of diabetes. Inclusion criteria required either IGT: 140-199mg/dl *or* IFG: 95-125mg/dl. Participants were required to be 25 year of age or older with a body mass index of 24 or greater. Participants were randomly assigned to one of the three following groups: Standard lifestyle plus Metformin (n=1073); standard lifestyle plus placebo (n=1082); intensive lifestyle modification (n=1079). Metformin was given at 850mg twice daily. Intensive lifestyle included a goal weight reduction of 7% of initial body weight through healthy diet and physical activity of moderate intensity for at least 150 minutes weekly (Knowler et.al, 2002, p. 394).

38% percent of the intensive lifestyle modification group maintained the 7% weight loss goal at time of publication. 58% had met the goal of 150 minutes of exercise per week. For those taking Metformin, 72% were able to accomplish 80% adherence to therapy. For those in the placebo group 77% were able to achieve 80% adherence to therapy (Knowler et al, 2002, p. 395-396).

The primary outcome for this study was the 3-year incidence of diabetes; defined by either a fasting glucose of greater than 126mg/dl or glucose greater than 200mg/dl after a 75-gram glucose load. The three-year incidence of diabetes was: 11 cases per 100 person years in the placebo group; 7.8 cases in the in the Metformin group; 4.8 in the intensive lifestyle modification group ($P < 0.05$). When

compared to placebo this rendered an incidence of diabetes percentage that was 58% lower (95% confidence interval: 48-66%) in the Intensive Lifestyle Modification group and 31% lower (95% CI: 17-43%) in the Metformin group. The 3-year incidence of diabetes was estimated to be 28.9% for the placebo group, 21.7% in the Metformin group and 14.4 in the Intensive Lifestyle group (Knowler, 2002, p. 398).

In summary, the Diabetes Prevention Program's study suggests that intense lifestyle modification with predetermined weight loss goals, dietary modification and 150 minutes of exercise per week is the superior approach to the prevention of diabetes in those with IGT and/or IFG. The study also suggests that Metformin is superior to placebo in the prevention of diabetes.

This strength of this study was its large size with subjects gathered from multiple care centers. This avoids social, gender or racial bias and allows for better generalization to other populations. Interventions and control groups were clearly defined. Participants were evenly distributed amongst the three randomized groups. Baseline characteristics such as gender, race, age, weight/BMI, and baseline physical activity were very evenly distributed. This reflects the benefit of a large-scale, randomized study. Optimal p-values and narrow confidence intervals rendered high statistical quality. Study personnel and participants were blinded if they were in the placebo or Metformin group. Incidence of diabetes was the primary measure of the study. Adherence was also addressed. Weight loss was another component that was evaluated but not included for purposes of this review. Each intervention was deemed safe and placed participants at minimal risk. Neither

Metformin nor intense lifestyle modification has been declared the standard of care for persons with prediabetes. Thus, participant groups were not denied a known, optimal care method. None of the interventions were serious threats to participant safety.

INDEPENDENT AND COMBINED EFFECTS OF EXERCISE TRAINING AND
METFORMIN

Malin, Chipkin, Gerber & Braun (2012) took a small sample size to quantitatively evaluate the combined effect of Metformin and exercise training. Outcome measures were changes in insulin sensitivity, serum insulin levels and fasting glucose levels over 12 weeks. Results were compared to each intervention individually. 32 participants in the Amherst, Massachusetts community were randomized equally into four groups: placebo; metformin; exercise training with placebo; exercise training with metformin. The study was conducted in a double-blind fashion. Participant inclusion criteria included an abnormal IGT. Exclusion criteria included smokers, those with recent significant weight changes and those with chronic disease such as respiratory, renal, and heart disease (p. 131-132).

Participants randomized into a Metformin group were gradually increased in dosing to 2,000mg daily. Compliance with placebo and metformin was greater than 90%. Participants randomized into an exercise-training group were subjected to supervised, structured exercise sessions of 60-75 minutes in duration, 3 times per week. Insulin sensitivity and serum insulin levels were monitored via systematic laboratory methods (Malin et.al, 2012, p. 132-133).

At the conclusion of the 12-week study, fasting glucose levels did not vary amongst the four groups. Serum insulin levels increased from 120.8pmol/L to 129.5pmol/L in the placebo group. Serum insulin levels decreased in every other group: Metformin – 144.4pmol/L to 100.8 pmol/L; exercise plus placebo – 83.1pmol/l to 73.1pmol/L; exercise plus Metformin – 92.9pmol/L to 75.8pmol/L (Malin et al. 2012, p. 135).

The most notable finding in the study, which is not included in other studies, was the decrease in insulin sensitivity when Metformin was added to the exercise group. Insulin sensitivity decreased in the placebo group: Ra – 12.97 to 10.89. Insulin sensitivity increased in both exercise alone: Ra – 9.20 to 14.12 and metformin alone: Ra 7.94 to 9.01. Insulin sensitivity was essentially unaffected in the combined exercise/metformin group: Ra – 11.08 to 11.42 (Malin et. al, 2012, p. 135).

Malin et. al (2012) propose that Metformin might have inhibited the benefits of insulin sensitivity in comparison to exercise alone. This hypothesis is derived from the fact that Metformin's mechanism of action directly inhibits normal cellular changes during exercise (p. 134). Malin et. al suggest exercise training is the primary mechanism in promoting increased insulin sensitivity in persons with IGT. Metformin, used alone or in combination with exercise, does benefit fasting glucose and serum insulin levels.

The study conducted by Malin et. al (2012) is limited by its small sample size and varied baseline statistics amongst the four groups. Though intensive insulin sensitivity and radiographic weight monitoring necessitates a small sample. The

quality of data through confidence interval was not readily available, also limiting its quality. Participants were randomized in double-blind fashion. All participants were followed through the conclusion of the 12-week study. There were more women in the placebo group; otherwise the groups were nearly equal from a gender perspective. It was noted that a large majority of participants were of Caucasian decent. The sample was derived from a small area of Massachusetts, so application to the general population is limited. Insulin sensitivity, fasting glucose and serum insulin were all statistically significant ($P < 0.05$) findings in the study.

ASIAN INDIAN DIABETES PREVENTION PROGRAMME

Ramachandran et. al's (2005) study note persons of Asian-Indian decent are genetically prone to IGT and insulin resistance at a young age despite lower than average body mass index (BMI). Persistent IGT was defined as impaired glucose tolerance on two separate glucose tolerance tests. 531 middle-class participants ages 33-55 were randomized into four groups: control; lifestyle modification; metformin; and lifestyle modification plus metformin. Metformin was started at 500mg twice-daily for 40 days but then decreased to 250mg twice-daily secondary to reported hypoglycemic symptoms. Lifestyle modification included education about appropriate diet and regular physical activity. The primary outcome was the 3-year incidence of diabetes, defined as fasting serum glucose of $>126\text{mg/dl}$ and/or 2 hour glucose $>200\text{mg/dl}$ following 75-gram glucose load.

502 of the subjects, 95%, completed the 3-year follow up. 44% developed diabetes (Ramachandran, 2005, p. 295). The control group's 3-year incidence of

diabetes is 55% (CI 95% 46.0 – 63.5). The incidence of diabetes in the lifestyle modification group is 39.3% with a relative risk reduction of 28.5% (CI 95% - 20.5-37.3. $p=0.018$) in comparison to control. The incidence of diabetes in the metformin group is 40.5% with a risk reduction of 26.4% (CI 95% - 19.1-35.1 $p=0.029$). The incidence of diabetes in the combined lifestyle modification-metformin group is 39.5% with a risk reduction of 28.2% (CI 95% - 20.3-37.0 $p=0.022$) (p. 293).

At the conclusion of the study, 81.5% of the lifestyle modification group adhered to dietary modifications, while 81.9% of the combined lifestyle modification-metformin group adhered to diet. Physical activity was adhered to by 58.8% by the lifestyle modification group while 62.9% of the combined lifestyle-metformin group adhered to the physical activity criteria. Lastly, 90.9% of the metformin group adhered to the drug regimen, while 95.1% of the combined lifestyle-metformin group adhered to the metformin regimen.

In summary, Ramachandran et.al (2005) suggest that lifestyle modification is the preferred approach in the prevention of diabetes in persons with IGT who are genetically prone to prediabetic states. A combined lifestyle modification and Metformin approach offers benefits that are slightly inferior to lifestyle modification. Metformin used alone offers significant benefits in comparison to placebo but are slightly less preferred in comparison to the lifestyle modification groups.

Ramachandran et.al's (2005) study is strong in its randomized, controlled format. However, it is not double blinded. The Asian-Indian population is culturally unique given the prevalence of IGT despite normal BMI. Thus, generalization

beyond the study population is hindered. The study included predominantly male subjects in all groups. Each group was composed of similar age categories. Unskilled/skilled workers were evenly predominant in all categories. Baseline fasting glucose and glucose tolerance, A1C and fasting insulin levels were similar in all groups (p. 292).

DISCUSSION

Increased screening for diabetes through the implementation of the *Affordable Care Act* will capture a large percentage of persons with undiagnosed prediabetes and type II diabetes. This potentiates a significant increase to the already burdensome financial costs the US already spends on the diabetes epidemic. Herman et.al (2012) found that 10 years of the *Diabetes Prevention Program* resulted in both lifestyle modifications and metformin being more cost-effective in comparison to placebo (p. 727). Furthermore, research is beginning to suggest that vascular effects of persistent, non-diabetic hyperglycemia have begun to progress. For these reasons, healthcare providers must strongly consider earlier screening and therapeutic intervention in the prevention of diabetes.

Adopting more expansive screening criteria should be considered a first step in achieving such goals. ACE/AACE joint recommendation looks to capture more persons at risk for diabetes. Meanwhile, the more widely utilized AHRQ recommends screening only when elevated blood pressure is present. This may not be in the best interest of the patient considering the progressing vascular

abnormalities in persistent hyperglycemic states. Therefore, healthcare providers should consider adopting ACE/AACE recommendations into practice.

When prediabetes is confirmed, the literature review recommends the implementation of lifestyle modifications as the first-line approach to prevent overt type II diabetes. Garber et.al (2008) suggest sustained weight loss of 5-10% (p. 938). Hamman et.al (2006) suggest that each 1kg of weight loss through intensive lifestyle modification may result in a 16% decrease in diabetes risk (p. 2105). To attain weight loss goals, physical activity of moderate intensity 30-60 minutes 5 days a week should be strongly encouraged. A diet of restricted calories, low-carbohydrate, high fiber, and low fat should also be encouraged (Garber, 2008, p. 938). The provider should collaborate on an individual basis with each patient in how to best achieve these outcomes with respect to cultural, social and individual lifestyle preferences.

Patients with prediabetes qualify for glucose screening biannual basis based on Medicare guidelines (Department of Health and Human Services, N.D.). At minimum this should guide follow up. In addition to glucose screening, patients with prediabetes should be monitored regularly for progression towards weight-loss goals. Discussion and encouragement surrounding adherence to lifestyle modifications such as diet and physical exercise should also take place.

While literature supports lifestyle modification is preferred as the first line approach, there are circumstances that Metformin is preferred. Metformin has shown to reduce fasting glucose levels and serum insulin levels in comparison to placebo. Metformin may be considered as first-line therapy in patients with

prediabetes who knowingly will not, or are physically unable to, adhere to lifestyle modifications. Starting Metformin may be further indicated in the presence of multiple comorbidities such as coronary artery disease, hypertension, obesity, hyperlipidemia once risks and benefits are considered. If, through continued follow up, lifestyle modification goals are not being met, a collaborative discussion regarding the risks and benefits of starting Metformin should take place.

Early legislation for increasing prediabetes resources is in progress. Representative DeGette has written legislation in 2011 for Medicare coverage of Medical Nutrition Therapy (MNT) for patients with prediabetes (Congressional Diabetes Caucus, 2011). MNT has proven effective in patients with diabetes and the concepts can be applied to individuals with prediabetes. Providers and the healthcare community must advocate for such legislation that expands services for the prevention of type II diabetes.

Research repeatedly supports physical activity as the optimal approach in the prevention of diabetes. The structure for physical activity varied in the literature. Research surrounding optimal regimens is warranted and should be advocated for. As research begins to promote such regimens, advocacy for insurance reimbursement for such programs should be supported. Standards for practice should then follow.

A fundamental value driving the *Affordable Care Act* is that all individuals have a right to healthcare. Implementation of the act is complicated by the excess cost of care in the current healthcare delivery system. To ensure sustainability during these seismic changes, different approaches to care must be considered. Any

changes that ensue must maintain quality outcomes the population expects.

Persistent treatment of treating diabetes with either lifestyle modifications or metformin meets these objectives by preventing costly treatment and management of diabetes while maintaining quality of life.

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