



Improvement in Cardiovascular Risk Markers with Glimepiride in Non Obese Subjects with Pre Diabetes: Similar to Obese Cohort Treated with Metformin

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Authors' contributions

This work was carried out in collaboration between both authors. Author UMK designed the study and wrote the protocol. Author RE performed the data collection, tabulated the data and assisted author UMK in statistical analyses, the review of the literature and preparation of the manuscript. Author UMK reviewed the reviewers' comments and revised the manuscript into the final version. Both authors read and approved the final manuscript.

Article Information

DOI: 10.9734/BJMMR/2016/29466

Editor(s):

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Complete Peer review History: <http://www.sciencedomain.org/review-history/16813>

Received 12th September 2016

Accepted 29th October 2016

Published 7th November 2016

Original Research Article

ABSTRACT

Background: We recently documented better efficacy of glimepiride in non obese subjects for delaying progression from Pre diabetes to type 2 diabetes as compared to metformin in obese subjects over duration of 5-9 years (mean, 7.2±0.2). Moreover, no deaths or adverse cardiovascular events occurred in either group and this finding may be attributed to beneficial changes in lipids and cardiovascular surrogate markers. However, the effects of interventions on lipids and cardiovascular surrogate markers were not reported.

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Objective: Therefore, Cardiovascular risk factors including Lipid fractions, e.g. serum Total cholesterol (TC), Triglyceride (TG), Low density Lipoprotein cholesterol (LDLC), High Density Lipoprotein Cholesterol (HDLC) and other markers, e.g. Homocysteine (HomC), highly sensitive C-Reactive Protein (CRP), Fibrinogen (FIBR) and Plasminogen Activator Inhibitor¹ (PAI1) were assessed prior to intervention and at interval of 6 months' in subjects with Pre diabetes; lean treated with glimepiride and obese administered metformin.

Subjects and Methods: 18 non obese subjects, 10 men and 8 women ages 27-78 years and 20 obese subjects, 10 men and 10 women with ages 32-81 years with Pre diabetes (fasting plasma glucose, 100 – 125 mg/dl and/or HbA1c, 5.7-6.4%) participated in the study. The study period was 5-9 years (mean, 7.2 ± 0.2). Non obese subjects received glimepiride and obese subjects were administered metformin. Subjects were counseled with lifestyle intervention (appropriate diet and exercise) at each visit during the study. Comparisons were conducted between lipids and CV markers at entry, at six months and at the last visit of the study for individual group as well as between groups for levels at baseline and at the end of the study period.

Results: In glimepiride group, marked improvements occurred in all parameters following treatment (Post Rx) at 6 months and were sustained till the end of the study HbA1C (%): 6.2 ± 0.2, 5.5± 0.1*, 5.7 ± 0.1*; TC (mg/dl): 212± 15, 174 ± 13*,178 ± 14*; TG (mg/dl): 202± 32, 162± 28*, 178± 14*; LDLC: 130± 12, 105± 10*, 109± 9*; Non HDLC(mg/dl): 181 ± 24, 130 ± 14*,109± 9*; HomC (µ Mol/l): 18± 3, 11± 2*, 12 ± 2*; CRP(Units): 13 ± 3, 6 ± 2*,5 ± 2*; FIBR (mg/dl): 403 ± 41, 296 ± 32*, 289± 28*; PAI¹ (ng/ml): 18 ± 4, 13 ± 3*, 12 ± 4*; Post Rx vs. Pre Rx, p<0.05 for all values]. HDLC was not significantly altered. Similar changes were also noted in obese subjects treated with metformin. No significant differences were also noted between 2 groups at the entry, 6 months or the end of study.

Conclusion: In subjects with Pre diabetes, glimepiride is as effective in improving lipid profiles and cardiovascular surrogate markers in nonobese when compared with metformin in obese subjects thus explaining similar cardiovascular outcomes in both groups.

Keywords: Pre diabetes; obese; lean; cardiovascular risk markers; Glimepiride; Metformin.

1. INTRODUCTION

We recently documented that treatment with glimepiride delayed the progression of Pre diabetes to type 2 diabetes in nonobese subjects for a significantly longer period as compared to administration of metformin in obese subjects followed over an average duration of 7.2 ± 0.2 years with a range of 5-9 years [1]. The same study also demonstrated a greater efficacy of glimepiride by delaying progression of Pre diabetes to type 2 diabetes in more nonobese subjects than obese subjects treated with metformin [1]. However, no deaths or cardiovascular events were encountered in either group. It is plausible that the effects of interventions on lipids and cardiovascular surrogate markers may have contributed to the cardiovascular safety, but were not reported. Therefore, we determined cardiovascular risk factors including the lipid profiles and other surrogate markers prior to and following therapy with glimepiride in nonobese and metformin in obese subjects with Pre diabetes.

2. SUBJECTS AND METHODS

The study assessed the efficacy of glimepiride, an insulin secretagogue on cardiovascular risk markers in non obese and metformin in obese subjects with Pre diabetes. The study was approved by the institutional review board and the human studies subcommittee at University of Iowa hospitals and clinics in Iowa City, Iowa, USA. The minimum number of subjects required to obtain statistical difference, p<0.05 between groups by power analysis was 15 in each group. Therefore, 18 non obese subjects (BMI <27 KG/M2), 10 men and 8 women ages 27-78 years and 20 obese subjects (BMI>27 KG/M2), 10 men and 10 women with ages 32-81 years with Pre diabetes presenting between July 1,1999 and June 30, 2002 participated in the study after obtaining informed consent. The diagnosis of Pre diabetes was confirmed by documentation of fasting plasma glucose, 100 – 125 mg/dl and/or HbA1c, 5.7-6.4% on 2 occasions at interval of 10-21 days according to the criteria established by American Diabetes Association [2]. Subjects with history of other disorders e.g. hypertension receiving drugs in the stable daily dose during

prior 3 months and women receiving oral contraceptives agents were included. The daily dose of the same medications was maintained throughout the study period. Subjects with serum liver enzymes, AST and ALT > 2 times normal; serum creatinine > 2 mg/dl and/or EGFR < 60 ml; abnormal serum free T4 and/or TSH levels and subjects receiving any antihyperlipidemic agents including statins were excluded. Pregnant women were excluded as well. Non obese subjects received glimepiride 1 mg once daily in the morning and obese subjects were administered metformin 1000 mg twice daily after breakfast and supper. Daily glimepiride dose of 1 mg was chosen in order to avoid hypoglycemia. Daily metformin dose of 2000 mg was elected as it is the established to be the maximum effective dose in type 2 Diabetes. Subjects were encouraged to comply with the therapeutic lifestyle intervention (appropriate diet and exercise) by counseling at each visit at the interval of 3 months for the 1st year and 6 months thereafter until the end of the study period over an average duration of 7.2 ± 0.2 years with a range of 5-9 years. HbA1c, Serum Total cholesterol (TC), Triglyceride (TG), Low density Lipoprotein cholesterol (LDLC), High Density Lipoprotein Cholesterol (HDLC), Homocysteine (HomC), highly sensitive C-Reactive Protein (CRP), Fibrinogen (FIBR) and Plasminogen Activator Inhibitor¹ (PAI¹) were determined in nonobese subjects with Pre diabetes prior to initiation of glimepiride and in obese subjects with Pre diabetes before administration of metformin and again at interval of 6 months through the study period. The laboratory tests were performed by the local clinical laboratory using analyzer and commercial

kits using well established methods provided by Siemens inc. Normal ranges for all tests were well established previously in adult men and women. Comparisons were conducted between lipids and CV markers at entry, at six months and at the last visit of the study for the individual group treated with either glimepiride or metformin. Comparisons were also performed between 2 groups administered glimepiride and metformin for the same serum concentrations at baseline and at the end of the study. Statistical methods used for comparisons between individual drug groups and between two drug groups were Paired student's 't' test and analyses of covariance respectively. The difference for comparison was considered statistically significant if 'p' value of <0.05 was attained.

All data are reported as Mean \pm SEM.

3. RESULTS

In glimepiride group, marked improvements occurred in all lipid fractions except HDL Cholesterol and all cardiovascular surrogate markers by 6 months with lowering of HbA1c and were sustained till the end of the study; $p < 0.05$ for all parameters except HDLC (Table 1). Similar improvements in all determinations were also noted in obese subjects treated with metformin, $p < 0.05$ for all determinations, the only exception being HDLC (Table 1). Finally, all the laboratory tests were not significantly different ($p > 0.05$) between subjects treated with glimepiride and those administered metformin at the entry, at 6 months or at the end of study period (Table 1).

Table 1. HbA1c, lipid fractions, Homocysteine (HomC), C-Reactive Protein (CRP), Fibrinogen (FIBR) and Plasminogen Activator Inhibitor 1 (PAI1) Prior to (Pre) and after (Post) Treatment (Rx) with Glimepiride (Glim) in Lean and Metformin (Met) in obese subjects with pre diabetes

	Met pre Rx	Met post Rx 6 months	Met post Rx last visit	Normal range	Glim pre Rx	Glim post Rx 6 months	Glim post Rx last visit
HbA1c (%)	6.1 \pm 0.2	5.4 \pm 0.1*	5.6 \pm 0.1*	<5.7	6.2 \pm 0.2	5.5 \pm 0.1*	5.7 \pm 0.1*
TC (mg/dl)	201 \pm 16	172 \pm 11*	166 \pm 12*	<200	212 \pm 15	174 \pm 13*	178 \pm 14*
TG (mg/dl)	197 \pm 38	168 \pm 19*	170 \pm 21*	<150	202 \pm 32	162 \pm 28*	156 \pm 22*
LDLC (mg/dl)	128 \pm 12	104 \pm 10*	98 \pm 8*	<100	130 \pm 12	105 \pm 10*	109 \pm 9*
HDLC (mg/dl)	32 \pm 6	36 \pm 7	35 \pm 5	40-59	31 \pm 7	34 \pm 7	37 \pm 6
Non HDLC (mg/dl)	167 \pm 21	134 \pm 13*	128 \pm 15*	< 130	181 \pm 24	130 \pm 14*	129 \pm 14*
HomC (μ Mol/l)	17 \pm 3	12 \pm 2*	11 \pm 2*	5.0-15.0	18 \pm 3	11 \pm 2*	12 \pm 2*
CRP (Units)	12 \pm 3	6 \pm 2*	5 \pm 2*	<5.0	13 \pm 3	6 \pm 2*	5 \pm 2*
FIBR (mg/dl)	388 \pm 36	291 \pm 28*	286 \pm 30*	200-400	403 \pm 41	296 \pm 32*	289 \pm 28*
PAI ¹ (ng/ml)	20 \pm 5	11 \pm 2*	12 \pm 3*	2-14	18 \pm 4	13 \pm 3*	12 \pm 4*

* $p < 0.05$ vs. Pre Rx

4. DISCUSSION

Pre diabetes is well established to be associated with increased overall mortality and morbidity for other the obese and the lean subjects with major contribution being attributed to cardiovascular disorders [3-11]. However, a recent report documented that the adverse outcomes including mortality were greater in subjects with Pre diabetes who progressed to diabetes when compared to those whose impaired glucose tolerance improved or normalized during the follow up period of 23 years [9]. Similar results have been reported in other studies as well [10,11].

The part of the data from this study documenting delay in progression to type 2 diabetes from Pre diabetes in lean subjects treated with glimepiride as well as obese cohort administered metformin has been reported previously [1]. In fact, in several subjects in both treatment groups, impaired glucose regulation normalized as expressed by HbA1c concentration (Table 1). Moreover, none of the subjects in both treatment groups experienced increased deaths due to any cause including cardiovascular disorders. Finally, other adverse cardiovascular outcomes were also not increased in both groups of subjects; namely, lean treated with glimepiride or obese administered metformin. The lack of occurrence of cardiovascular events as well as cardiovascular and all-cause mortality may be attributed to improvement in glycemic indices as well as adversely altered lipid fractions (serum total cholesterol, triglycerides and LDL Cholesterol concentrations) as well as the circulating levels of surrogate markers of adverse cardiovascular outcomes in both groups of subjects with Pre diabetes, lean treated with glimepiride and obese administered metformin. This finding is consistent with the data in the literature showing similar changes in lipid fractions and cardiovascular surrogate markers as well as reduction in cardiovascular morbidity/mortality and all cause mortality with various interventions in subjects with Pre diabetes [12-23].

However, none of the interventions in these previous studies included glimepiride or any other insulin secretagogue. The beneficial effect of glimepiride may be attributed to the decline in insulin secretion as the major pathophysiologic factor in onset of Pre diabetes in the lean subjects in contrast to insulin resistance in obese as documented in our recent study and several previous reports [24-28]. Moreover, the

improvement in laboratory parameters noted in this study is also in conformity with several previous reports documenting similar benefits following administration of glimepiride in conjunction with therapeutic life style change in subjects with type 2 diabetes [23-27]. Therefore, the absence of cardiovascular events including deaths among both groups of subjects, lean treated with glimepiride and obese administered metformin. May be attributed to improvement in glycemic control as well as serum lipid profiles and well established cardiovascular risk factors as documented in several previous clinical trials conducted in large populations as well as meta analyses [12-23]. However, our finding deserves confirmation by a similar study with a larger population.

5. CONCLUSION

In conclusion, in subjects with Pre Diabetes, glimepiride is effective in improving lipid profiles and cardiovascular surrogate markers in nonobese subjects whereas metformin exerts a similar influence in obese subjects thus explaining similar cardiovascular outcomes in both groups.

ETHICAL APPROVAL

Both authors hereby declare that the study design, the protocol, the informed consent form, the procedures and methods used for statistical analyses were reviewed and approved by the institutional review board and the human studies subcommittee at University of Iowa hospitals and clinics in Iowa City, Iowa, USA in conformity with the ethical standards laid down in the 1964 Declaration of Helsinki.

DISCLAIMER

The abstract was presented at Annual Endocrine Society Meeting in March 2015 in San Diego, CA and was published in the proceedings of the meeting.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Kabadi UM. Comparative efficacy between glimepiride and metformin in preventing progression of prediabetes to type 2

- diabetes. *Journal of Diabetes Mellitus*. 2013;3(3):129-133.
2. American Diabetes Association. Classification and Diagnosis of Diabetes; *Diabetes Care* 2016;39(Suppl. 1):S513-522.
 3. Schnell O, Standl E. Impaired glucose tolerance, diabetes, and cardiovascular disease. *Endocr Pract*. 2006;12(Suppl 1): 16-9.
 4. Selvin E, Steffes MW, Zhu H, et al. Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. *N Engl J Med*. 2010;362(9):800-11.
 5. Kowall B, Rathmann W, Heier M et al. Categories of glucose tolerance and continuous glycemic measures and mortality. *Eur J Epidemiol*. 2011;(8):637-45.
 6. Anselmino M, Sillano D. Impact of pre-diabetes and diabetes on cardiovascular outcomes. *Curr Vasc Pharmacol*. 2012; (6):680-3.
 7. Huang Y, Cai X, Chen P, et al. Associations of prediabetes with all-cause and cardiovascular mortality: A meta-analysis. *Ann Med*. 2014;46(8):684-92.
 8. Gordon-Dseagu VL, Mindell JS, Steptoe A, et al. Impaired glucose metabolism among those with and without diagnosed diabetes and mortality: A cohort study using health survey for England data. *PLoS One*. 2015;10(3):e0119882.
 9. Yali An, Ping Zhang, Jinping Wang, et al. Cardiovascular and all-cause mortality over a 23-year period among Chinese with newly diagnosed diabetes in the Da Qing IGT and diabetes study diabetes care. 2015;38(7):1365-1377.
 10. Gong Q, Zhang P, Wang J, et al. Changes in mortality in people with IGT before and after the onset of diabetes during the 23-year follow-up of the Da Qing diabetes prevention study. *Diabetes Care*; 2016. DOI: 10.2337/dc16-0429
 11. Mudaliar U, Zabetian A, Goodman M, et al. Cardio metabolic risk factor changes observed in diabetes prevention programs in US settings: A systematic review and meta-analysis. *PLoS Med*. 2016;13(7): e1002095.
 12. Dumasia R, Eagle KA, Kline-Rogers E, et al. Role of PPAR- gamma agonist thiazolidinediones in treatment of pre-diabetic and diabetic individuals: A cardiovascular perspective. *Curr Drug Targets Cardiovasc Haematol Disord*. 2005;5(5):377-86.
 13. Del Prato S, Bianchi C, Miccoli R, et al. Pharmacological intervention in prediabetes: Considering the risks and benefits. *Diabetes Obes Metab*. 2007; 9(Suppl. 1):17-22.
 14. Cubbon R, Kahn M, Kearney MT. Secondary prevention of cardiovascular disease in type 2 diabetes and prediabetes: A cardiologist's perspective. *J Clin Pract*. 2008;62(2):287-99.
 15. Hopper I, Billah B, Skiba M, et al. Prevention of diabetes and reduction in major cardiovascular events in studies of subjects with prediabetes: Meta-analysis of randomized controlled clinical trials. *Eur J Cardiovasc Prev Rehabil*. 2011;18(6):813-23.
 16. Griffin SJ, Borch-Johnsen K, Davies MJ, et al. Effect of early intensive multifactorial therapy on 5-year cardiovascular outcomes in individuals with type 2 diabetes detected by screening (ADDITION-Europe): A cluster-randomized trial. *Lancet*. 2011;378(9786):156-67.
 17. Krysiak R, Gdula-Dymek A, Okopień B. Effect of metformin on selected parameters of hemostasis in fenofibrate-treated patients with impaired glucose tolerance. *Pharmacol Rep*. 2013;65(1):208-13.
 18. Perreault L, Temprosa M, Mather KJ, et al. Diabetes prevention program research group. Regression from prediabetes to normal glucose regulation is associated with reduction in cardiovascular risk: Results from the Diabetes Prevention Program outcomes study. *Diabetes Care*. 2014;37(9):2622-31.
 19. DiNicolantonio JJ, Bhutani J, O'Keefe JH. Acarbose: Safe and effective for lowering postprandial hyperglycemia and improving cardiovascular outcomes. *Open Heart*. 2015;2(1):e000327.
 20. Sepah SC, Jiang L, Peters AL. Long-term outcomes of a Web-based diabetes prevention program: 2-year results of a single-arm longitudinal study. *J Med Internet Res*. 2015;17(4):e92.
 21. Herman WH, Ye W, Griffin SJ, Simmons RK, et al. Early detection and treatment of type 2 Diabetes reduce cardiovascular morbidity and mortality: A simulation of the results of the Anglo-Danish-Dutch study of intensive treatment in people with Screen-

- Detected Diabetes in Primary Care (ADDITION-Europe). *Diabetes Care*. 2015; 38(8):1449-55.
22. De Kreutzenberg SV, Ceolotto G, Cattelan A, et al. Metformin improves putative longevity effectors in peripheral mononuclear cells from subjects with prediabetes. A randomized controlled trial. *Nutr Metab Cardiovasc Dis*. 2015;25(7): 686-93.
 23. Stevens JW, Khunti K, Harvey R, et al. Preventing the progression to type 2 diabetes mellitus in adults at high risk: A systematic review and network meta-analysis of lifestyle, pharmacological and surgical interventions. *Diabetes Res Clin Pract*. 2015;107(3):320-31.
 24. Derosa G, Mugellini A, Ciccarelli L, et al. Comparison between repaglinide and glimepiride in patients with type 2 diabetes mellitus: A one-year, randomized, double-blind assessment of metabolic parameters and cardiovascular risk factors. *Clin Ther*. 2003;25(2):472-84.
 25. Tsunekawa T, Hayashi T, Suzuki Y, et al. Plasma adiponectin plays an important role in improving insulin resistance with glimepiride in elderly type 2 diabetic subjects. *Diabetes Care*. 2003;26:285-289.
 26. Kabadi UM. Cost-effective management of hyperglycemia in patients with type 2 diabetes using oral agents. *Managed Care*. 2004;48-59.
 27. Kabadi MU, Kabadi UM. Effects of glimepiride on insulin secretion and sensitivity in patients with recently diagnosed type 2 diabetes mellitus. *Clin Ther*. 2004;26(1):63-9.
 28. Kabadi UM. major pathophysiologic factor in prediabetes and type 2 diabetes mellitus: Decreased insulin secretion in lean and insulin resistance in obese subjects, Annual Meeting, Endocrine Society; 2016.

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