

Study on the effect of oral hypoglycaemic agents on arterial stiffness among Malays with type II diabetes mellitus

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Abstract

Objective: To determine the effect of two regimens of oral hypoglycaemic agents: sulphonylurea monotherapy and metformin in combination with sulphonylurea on arterial stiffness. **Methods:** A case control study was conducted at the Family Medicine and Diabetic Clinic, HUSM from May 2004 until May 2005. Sixty subjects receiving sulphonylurea alone and ninety subjects on combination therapy with metformin participated in this study. A simple random sampling method using a draw lot was used to select 51 subjects for each group. Augmentation index (AI) was measured using the Sphygmocor apparatus and all measurements were performed by the investigators after an earlier validation study. The mean augmentation index measurements were analyzed. **Results:** The mean AI values of diabetic subjects treated with sulphonylurea monotherapy and a combination with metformin were 140.51 ± 11.42 vs 140.14 ± 12.86 , $p = 0.877$. AI values were significantly higher in females compared with males (143.23 ± 10.60 vs 135.82 ± 13.01 , 95% CI: -12.07, -2.73, $p = 0.002$). Duration of diabetes (in years) was significantly less (3.46 ± 3.16 vs 5.41 ± 3.66 , $p = 0.005$) for sulphonylurea monotherapy patients compared with combination therapy patients. **Conclusion:** This study shows that sulphonylurea monotherapy and metformin in combination with sulphonylurea have similar effects on arterial stiffness in type 2 diabetes subjects. Diabetes is associated with a greater arterial stiffness in women compared with men.

Keywords: arterial stiffness, augmentation index, oral hypoglycemic agent

Introduction

Insulin resistance and type 2 diabetes are major causes of morbidity and mortality in the industrialized world. It has been estimated that the prevalence of type 2 diabetes mellitus will increase from the present 160 million to 215 million by 2010.¹ Of the patients diagnosed with myocardial infarction, about 20% have previously had type 2 diabetes.²

Arterial stiffness may become a major primary goal of treatment in patients at risk of cardiovascular disease. Drugs may improve the stiffness of the arterial wall through either functional or structural mechanisms.³

Arterial stiffness is determined by structural and functional components related to the intrinsic elastic properties of the artery. The endothelium, the elastic tissue within the intima media layer and smooth muscle contribute to arterial stiffness.⁴

The relationship between arterial stiffness as measured by pulse wave velocity (PWV) and the elastic properties of the arterial wall has been extensively studied.⁵ Radial artery pressure waveforms recorded with tonometry have been

shown to equal those measured intra-arterially in a large group of healthy subjects.⁶ Several studies have now demonstrated that a single generalized transfer function can be used to determine accurately central from peripheral pressures in healthy subjects and in patients with a variety of diseases.^{7,8,9}

In a study by Satoh *et al*,¹⁰ it was demonstrated that treatment of patients with type 2 diabetes with pioglitazone for three months resulted in a significant decrease in PWV.¹⁰ This is in agreement with other studies which reported that intima media thickness (IMT) was significantly reduced in type 2 diabetic patients administered troglitazone or pioglitazone for three months.^{11,12}

However, there is lack of clinical data on the effect of conventional oral hypoglycemic agents, like metformin or sulfonylurea or a combination of both, on arterial stiffness in patients with type 2 diabetes mellitus although there is a study showing that treatment with metformin for 12 weeks improved endothelial function.¹³

The aim of the study was to examine combined oral hypoglycaemic agent therapy on arterial stiffness in type 2 diabetes. Based on previous studies, this study also took three months as a minimum duration for taking the oral hypoglycaemic agent(s).

Methodology

This investigation was a case control study, between groups of Malay diabetic patients attending Family Medicine and

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Diabetic Clinica at HUSM from May 2004 till May 2005. One group was treated with sulphonylurea alone and another group was treated with a combination of metformin and sulphonylurea. A simple random sampling method using draw lots was used for both groups.

Criteria for both study groups

Inclusion criteria

1. Malays
2. Male or female subjects with type 2 diabetes mellitus
3. Age 40 to 65 years at recruitment
4. Subjects taking oral hypoglycemic agents (sulphonylurea alone or with metformin) for at least 3 months.

Exclusion criteria

1. Non-Malay
2. Concomitant hypertension
3. Factors which make the measurement of arterial stiffness by PWA difficult such as atrial fibrillation and significant peripheral vascular disease.
4. Subjects with macrovascular disease

Sample size calculation

Sample size was calculated based on two mean proportions with an expected mean difference set to five with SD 8.19 (based on AI in The Chennai Urban Population Study¹⁴ {CUPS-9}) plus 20% dropout. The minimum samples needed are 51 in each group.

Pulse wave analysis

The augmentation index (AI) is derived from systolic pulse wave analysis. The AI measured from the radial artery also correlates with carotid artery intima-media thickness in diabetic and non-diabetic subjects and predicts coronary artery disease independent of other risk factors.¹⁴

Measurement was by applanation tonometry using an automated SphygmoCor machine. The volume and pressure displacement which occurs in the artery was captured by the high fidelity probe. This was converted into a trace of the pulse contour on the computer screen. Using a transfer factor, this was converted to give figures and a graph which depict the central aortic pressure. Aortic stiffness is measured as a percentage. The mean of two measurements, each consisting of 15-20 sequentially recorded radial artery waveforms, was taken. In this study, AI measured by a SphygmoCor machine was considered as an index of arterial stiffness.

Validation study

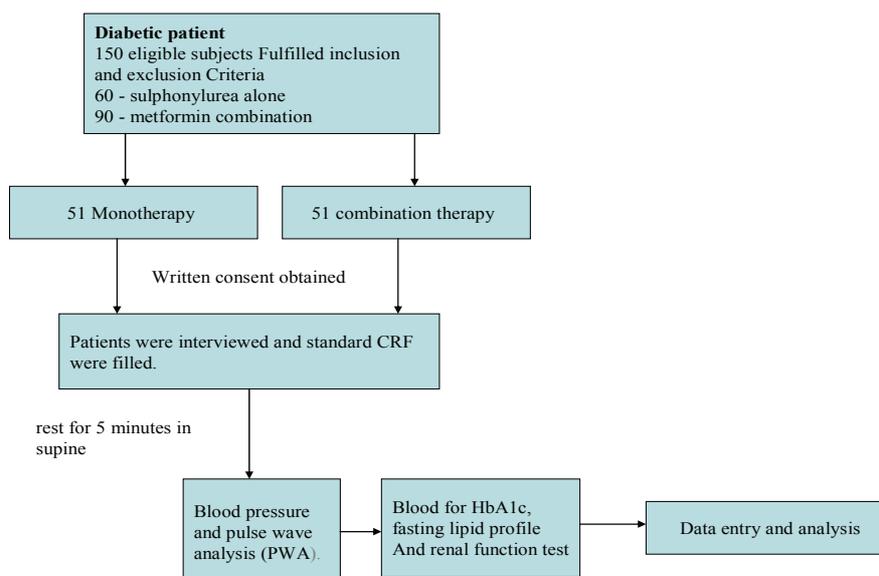
The arterial stiffness was assessed by measuring AI at the radial artery. To check for the reproducibility of the augmentation index, two measurements were performed on 20 subjects on consecutive days by the same observer. The mean difference in AI between the first and second measurements was 2.6 and the coefficient variance (CV) was 2.47.

Study protocol

The protocol for this study was approved by the School of Medical Sciences Research and Ethical Committee. All subjects gave written informed consent. Other parameters such as blood pressure, body mass index (BMI), HbA1c and fasting lipid profile were documented.

Statistical analysis

All data were analyzed using the Statistics Program for Social Sciences (SPSS) software (version 12.1). Mean and standard deviation were calculated for numerical data. Independent *t*-test or analysis of variance as appropriate was used for comparing mean values of selected variables in both groups. Analysis of covariance (ANCOVA) was used



to compare the means and to adjust for confounding variables. ANOVA test was used for comparing more than two mean values of selected variables. In all statistical analyses, $p < 0.05$ was considered as statistically significant at a confidence interval of 95%.

Results

A total of 51 respondents on sulphonylurea monotherapy and 51 respondents on a combination metformin and sulphonylurea therapy were recruited. The mean difference in duration of diabetes between the two groups was statistically significant. However, there was no significant difference in mean augmentation index between two regimens of oral hypoglycaemic agents: sulphonylurea monotherapy and metformin in combination with sulphonylurea therapy ($p = 0.812$). Table 1 demonstrates the clinical features while Table 2 shows the comparison of augmentation indices among the study groups.

In diabetes mellitus, the AI values were significantly higher in females compared with males (143.23 ± 10.60 vs 135.82 ± 13.01 , 95% CI: -12.07, -2.73, $p = 0.002$) as shown in Table 3 and it was still significant even after correcting for potential confounders, such as BMI, waist circumference, smoking status, systolic and diastolic blood pressure ($p = 0.016$).

Discussion

Vascular disease is a major cause of morbidity and mortality among patients with diabetes mellitus. Abnormalities in endothelium-dependent vascular responses have been reported among patients with type 2 diabetes.¹⁵ In a study by Mather *et al.*, which assessed the effect of metformin on impaired endothelial function in type 2 diabetes mellitus using forearm plethysmography, it was reported that 12 weeks of metformin (500 mg twice daily) significantly improved both insulin resistance and endothelial function.¹³

However, this study found that there was no significant difference in mean augmentation index between metformin in combination with sulphonylurea therapy and sulphonylurea monotherapy. The difference was not significant, most probably because the control of diabetes was similar in both groups.

Several studies have suggested that women tend to lose their protection from cardiovascular disease relative to men if they become diabetic.^{16,17,18} This was supported by our finding. Female subjects had stiffer arteries compared to male subjects and this difference was statistically significant. This result was, however, in contrast to that of Avolio *et al.* who found no difference between genders.¹⁹

Table 1: Clinical features of the study population

Variables	Sulphonylurea monotherapy (n = 51)	Metformin in combination with sulphonylurea therapy (n=51)	p value
Age (yrs)	49.90 ± 6.03	50.12 ± 5.63	0.852
Body mass index (kg/m ²)	25.84 ± 4.34	26.26 ± 4.49	0.590
Waist circumference (cm)	84.21 ± 9.48	85.30 ± 8.12	0.534
Systolic blood pressure (mmHg)	123.47 ± 9.64	123.73 ± 9.89	0.895
Diastolic blood pressure (mmHg)	74.51 ± 4.95	76.27 ± 5.39	0.088
Duration of diabetes (years)	3.46 ± 3.16	5.41 ± 3.66	0.005
HbA1c (%)	9.19 ± 2.49	9.48 ± 2.10	0.540
Serum Cholesterol (mmol/L)	5.43 ± 0.88	5.69 ± 1.01	0.159
LDL Cholesterol (mmol/L)	3.09 ± 1.09	3.44 ± 0.91	0.076
Serum triglyceride (mmol/L)	2.02 ± 1.09	2.08 ± 0.99	0.754
HDL cholestrol (mmol/L)	1.39 ± 0.54	1.29 ± 0.32	0.263
AI (%)	140.51 ± 11.42	140.14 ± 12.86	0.877
Non-smoker	37 (72.5%)	38 (74.5%)	–
Smoker	4 (7.9%)	7 (13.7%)	–
Ex-smoker	10 (19.6%)	6 (11.8%)	–

* Independent t-test; mean (sd)

Table 2: Comparison of augmentation index between two group regimens of oral hypoglycaemic agents

Subjects	Mean	Mean difference	p value
monotherapy (n = 51)	⁰ 140.51 ± 11.42	0.37	¹ 0.877
Combination therapy (n = 51)	⁰ 140.14 ± 12.86	(-4.40, 5.15)	
monotherapy (n = 51)	² 138.77	0.55	³ 0.812
Combination therapy (n = 51)	² 138.22 (134.48, 141.96)	(-4.02, 5.12)	

⁰ Mean with standard deviation

¹ Independent t-test applied

² Adjusted mean difference with 95% confidence interval (Bonferroni adjustment applied)

³ ANCOVA applied (adjusted for confounding factors such as age, smoking status and duration of diabetes)

Table 3: Comparison of augmentation index between gender

Subjects	Mean	Mean difference (95% CI)	P value
Male (n = 40)	^o 135.82 ± 13.01	-7.401	¹ 0.002
Female (n = 62)	^o 143.23 ± 10.60	(-12.07, -2.73)	
Male (n = 40)	² 135.99 (131.83, 140.15)	6.67	³ 0.016
Female (n = 62)	² 142.66 (138.34, 146.98)	(-12.07, -1.26)	

^o Mean with standard deviation

¹ Independent t-test applied

² Adjusted mean difference with 95% confidence interval (Bonferroni adjustment applied)

³ ANCOVA applied (adjusted for confounding factors such as BMI, waist circumference, smoking status, systolic and diastolic blood pressure.)

Lehman *et al* also observed stiffer carotid arteries and aortas in women, but not in men, with IDDM compared with non-diabetic individuals. Similar gender-specific results have been found for aortic PWV in patients with NIIDM.²⁰ In the ARIC study, the correlation of glucose and insulin with stiffness of the carotid artery also tended to be higher in women than in men.²¹

The presence of diabetes imposes a greater risk of cardiovascular events in women compared with men and the present results are consistent with increased relative risk in women with diabetes compared with men.²²

However, this study did not address the possible mechanisms by which diabetes could accelerate age-related stiffening of the aorta in women but not in men. Estrogen affects connective tissue structure through a variety of mechanisms, and in post-menopausal women, hormone replacement therapy is associated with reduced arterial stiffness in non-diabetic postmenopausal women²³ but not in post-menopausal women with diabetes.²⁴

Conclusion

This study has demonstrated that metformin in combination with sulphonylurea and sulphonylurea monotherapy have similar effects on arterial stiffness in type 2 diabetic subjects. However, diabetes is associated with a greater stiffening of the arteries in women compared to men and this is not explained by hypertension. Although two different groups of oral hypoglycaemic agents showed no difference in augmentation index, further larger studies are needed to look at the effect of the drugs, which can be relevant to clinical outcomes.

Limitation

The study population was small when comparing different regimens of oral hypoglycaemic agents. This small number of subjects might affect the results that were obtained and the subjects being studied might not be representative. Drug compliance was not examined in this study. Prescribed medications were not always taken and this fact could affect the results of this study.

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