THE NEW ARMENIAN MEDICAL JOURNAL
Vol.13 (2019), No 4, p.68-76

ADIPONECTIN AND ADMA LEVEL IN TYPE-2 DIABETES PATIENTS AFTER 12 WEEKS OF TREATMENT WITH GLIMEPIRIDE AND METFORMIN FIXED DOSE COMBINATION (DIAGRAM STUDY)

Soelistijo S.A.[2*], Ardiany D.[1], Tjokroprawiro A.[2]

[1]Department of Internal Medicine, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo General Hospital Surabaya, Indonesia

[2]Division of Endocrinology and Metabolism, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo General Hospital Surabaya, Indonesia

Received 15.12.2018; accepted for printing 15.10.2019

Abstract

Background: Recent published study on glimepiride showed remarkable increase of plasma adiponectin while metformin was associated with a decrease in asymmetric dimethylarginine concentrations. A fixed-dose combination of glimepiride and metformin available in Indonesia with limited local data on plasma hba1c adiponectin and asymmetric dimethylarginine concentrations.

Objective: This clinical trial aimed to evaluate the effect of fixed-dose combination of 1 mg glimepiride and 250 mg metformin Immediate Release on the level of plasma adiponectin, circulating asymmetric dimethylarginine, ankle-brachial pulse wave velocity, as well as fasting blood glucose and hba1c change in 40 patients with type 2 diabetes mellitus after 12 weeks of therapy.

Methods: Diagram was an open label study. We compared pre- and post-treatment values of high molecular weight adiponectin and asymmetric dimethylarginine level after 12 weeks treatment period with fixed-dose combination glimepiride/metformin. Forty patients with type 2 diabetes mellitus aged 40 – 60 years who were not currently treated with any Oral Anti Diabetic agents, statins, angiotensin converting enzyme inhibitors and/or angiotensin receptor blockers for at least 8 weeks and the hba1c value between 7% and <10% have been enrolled for this clinical trial.

Results: Fixed Dose Combination glimepiride/metformin is proven effective for treating forty patients with type-2 diabetes who were included in this study, even though plasma adiponectin was not significantly increased (34 ng/mL; p=0.201) by the administration of this fixed-dose combination for a 12 weeks treatment period as expected, however the treatment effect in increased adiponectin was shown in subjects with adiponectin dysfunction. Significant increase of asymmetric dimethylarginine median value (0.14 µmol/L, p<0.001) and decrease of ankle-brachial pulse wave velocity (-110.4 cm/sec, p=0.016) were shown in this study accompanied by the decrease in hba1c from 8.52% to 7.38% (p<0.001) and fasting blood glucose from 165.9 mg/dL to 123.1 mg/dL (p<0.001). Mild adverse events were reported in 7.5% patients, while serious adverse event was reported in one subject and was not related to study drug.

Conclusion: It can be concluded that treatment with fixed-dose combination glimepiride/metformin has effect in improving endothelial function by increasing adiponectin and lowering ankle-brachial pulse wave velocity level significantly. Meanwhile, the administration of fixed-dose combination glimepiride/metformin may not have effect in decreasing ADMA level. Further studies which included larger population with more varied parameters are needed to confirm the relationship of this fixed-dose combination with other factors.

Keywords: *diabetes mellitus type 2, amaryl M, adiponectin*

Introduction

The number of patients with type 2 diabetes mellitus world-wide has increased rapidly in the past several decades due to several factors, such as the advancing age of the population and life-style changing [*Nathan DM, 2002*]. Hyperglycemia has been associated with their increased risk of cardiovascular diseases aside from the contribution of

Address for Correspondence:
Soebagijo Adi Soelistijo
Division of Endocrinology and Metabolism, Department of Internal Medicine, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo General Hospital, Jalan Mayjend Prof. Dr. Moestopo 6 – 8 Surabaya 62086, Indonesia
Tel.: +62315501617
E-mail: soebagijo@yahoo.com

other mechanisms such as decrease of plasma adiponectin and increase of circulating asymmetric dimethylarginine (ADMA) [*Hotta K et al., 2000*].

Low plasma adiponectin level is significantly correlated to endothelial dysfunction due to its insulin-sensitizing effects as well as antiatherogenic properties [*Gottsater A et al., 2004, Han SH et al., 2007*]. Meanwhile increased ADMA may contribute to the development of insulin resistance and coronary heart disease [*Chan NN, Chan JC, 2002, Lajer et al., 2008*]. ADMA is a mediator of endothelial dysfunction and a marker of vascular disease that is intimately involved in the pathogenesis of hypertension and atherosclerosis. Patients with type-2 diabetes mellitus are well known to have decreased levels of plasma aadiponectin and increased level of plasma ADMA [*Hotta K et al., 2000*]. Glimepiride, a third generation sulfonylurea agent, may increase the level of adiponectin in elderly patients with type 2 diabetes. Metformin could decrease the level of ADMA by increasing haemodynamic responses to L-arginine, the precursor of vasodilatory nitric oxide (N0) [*Correia S et al., 2008*].

Carotid-femoral Pulse Wave Velocity (cfPWV) has been shown to be a reliable predictor of cardiovascular risk in hypertensive patients. Recently, an instrument has been developed which allows the measurement of brachial-ankle pulse wave velocity (baPWV) using pressure cuffs wrapped around the brachium and ankle [*Liu H et al., 2005; Meguro T et al., 2009; Wang CP et al., 2009*]. Occlusion and monitoring cuffs were placed around both sides of the upper and lower extremities, and pressure waveforms of the brachial and tibial arteries were recorded. baPWV may offer more technical simplicity and a shorter sampling time than the previous method [*Imanishi R et al., 2004*].

A fixed-dose combination of Glimepiride and Metformin available in Indonesia. It has been proven that this fixed dose combination is bioequivalent to its two separated components. Another study has also demonstrated that this fixed dose combination glimepiride/metformin is equally safe and effective for the treatment of T2DM compared to the combination of both drugs given separately [*Asagam T et al., 2002; Tsunekawa T et al., 2003; Baik S, 2005; Yu K, 2005; Koshiba K et al., 2006;*]. This clinical trial aimed to evaluate the effect of fixed dose combination of 1 *mg* glimepiride and 250 *mg* metformin IR on the level of adiponectin and ADMA as well as baPWV change in patients with type 2 diabetes mellitus after 12 weeks of therapy. In addition, this study also aimed to evaluate its effect on glycemic improvement as well as the change of Tumo necrosis factor alfa (TNF-α), homeostatic model assessment for insulin resistence (HOMA-IR) and for β-cell function (HOMA-β).

Material and Methods

In this open label study, 40 patients with type 2 diabetes mellitus aged 40 – 60 years who were not currently treated with any OAD agents, statins, ACE inhibitors and or ARBs for at least 8 weeks and with *hba1c* between 7% and <10% have been enrolled. Written informed consents were obtained from the patients before participation in the study.

The level of plasma high molecular weight (HMW) adiponectin and ADMA, baPWV were measured at baseline, after 8 week, and 12 week treatment with fixed dose combination glimepiride/metformin.

All patients started to take their treatment with dose of 1 tablet (1mg glimepiride and 250 *mg* metformin Immediate Release (IR)) per day administered with breakfast or with the first main meal of the day. Dosage was titrated based on the result of patient fasting blood glucose fasting blood glucose (FBG) test by increasing the dose or frequency. If taken twice per day, fixed dose combination glimepiride/metformin should be administered with breakfast or with the first main meal of the day and the evening meal.

The primary outcome is the improvement of HMW adiponectin and ADMA level after 12 week treatment with fixed dose combination glimepiride/metformin. Secondary outcome are the improvement of baPWV after 12 week treatment with fixed dose combination glimperide/metformin, glucose control as measured by FBG and *hba1c*, changes of TNFα level, homeostasis model of insulin resistance, homeostasis model of beta cell function.

Descriptive analysis was performed on the database. Qualitative data was summarized in frequency tables, and quantitative data was summarized in quantitative descriptive statistics (frequency, mean, standard deviation, median, range). Statistical analyses were conducted with the SPSS software version 11.5.

RESULTS

The total of 40 patients were included in this study. Mean ± SD of age, BMI, waist circumference, systolic, and diastolic blood pressure were 51.3 ± 5.5 years; 26.7 ± 4.6 *kg/m²*, 88.6 ± 10.9 *cm*, 131.8 ± 17.1 *mmHg*, and 85.2 ± 8.8 *mmHg*, respectively. Median duration of type 2 diabetes since diagnosis was 5 years with a wide range from 0 to 84 months. Mean ± SD of *hba1c* and baPWV were 8.5 ± 0.9 % and 1625.5 ± 295.5 *cm/sec* respectively. Median FBG, HMW adiponectin, ADMA, TNF-α, fasting insulin, HOMA-IR, and HOMA-β were, 153.5 (79.0-366.0) *mg/dL*, 1712.0 (88.0-6673.0) *ng/mL*, 0.6 (0.1-1.4) *µmol/L*, 2.2 (0.9-71.7) *pg/mL*, 8.2 (1.5-27.0) *µIU/mL*, 2.87 (0.74-10.21)%, and 36.56 (3.51-355.50)% respectively (Table 1).

Before switching to fixed dose combination glimepiride/metformin, 22 of 40 subjects (55%) were not relied on OAD, around 42.5% subjects used sulphonylurea as their main OAD and 2.5% subjects used biguanide. Most of the subjects have finished taking medication for 12 weeks. Four subjects were lost to follow up, while one subject dropped out from the study at the last visit due to serious adverse event of thrombotic infarct (Table 2).

Figure 1A shows that there was a trend of increase in HMW adiponectin level, even though it was not statistically significant (p=0.201), while Figure 1B shows significant increase of ADMA median value (0.14, p<0.001) after 12 weeks.

Figure 1C shows a significant decrease of baPWV (p=0.016) after 12 weeks. TNF-α was not significantly affected by the administration of study drug with p=0.334 at the 12 week visit (Figure 1D). The measurement of TNF-α resulted in a very heterogenic data with many outliers, especially at the baseline data.

Figure 1E shows a significant decrease of Homa-IR (p=0.003), while Figure 1F shows a significant increase of Homa-β (p=0.001) at 12 week of study treatment.

Fasting blood glucose decreased continuously throughout the study period with p<0.001. The decrease of FBG was more pronounced in the first 4 weeks of treatment and after that it tended to flatten (see Figure 1G). The Figure 1Hshows a statistically significant decrease of *hba1c* (p<0.001) from 8.52% to 7.38% after 12 weeks of study treatment.

The incidence of adverse events was low in this study. Only 3 of the 40 (7.5%) patients experienced mild adverse events that diminished without any corrective treatment, except for nausea hat used standard medication. All subjects were resulted with recovery. Types of adverse events experienced by subjects were palpebral edema which was experienced by one subject, elevated ALT by one subject, and nausea and dermatological reaction by another subject.

TABLE 1.

Demographic and baseline of intention to treat population (n = 40)

Variables	Statistics
Age (years)	51.3 ± 5.5
Male, n(%)	16 (40.0)
Female, n (%)	24 (60.0)
BMI (*kg/m2*)	26.7 ± 4.6
Waist circumference (*cm*)	88.6 ± 10.9
Systolic BP (*mmHg*)	131.8 ± 17.1
Diastolic BP (*mmHg*)	85.2 ± 8.8
Type 2 DM median duration (months)	60.0 (0.0 – 84.0)
Median of fasting blood glucose (*mg/dL*)	153.5 (79.0 – 366.0)
HbA1C (%)	8.5 ± 0.9
Median of HMW adiponectin (*ng/mL*)	1736.0 (88.0 – 6673.0)
Median of ADMA (*µmol/L*)	0.6 (0.1 – 1.4)
Median of TNF-α (*pg/mL*)	2.2 (0.9 – 71.7)
Median of fasting insulin (*µIU/mL*)	8.2 (1.5 – 27.0)
baPWV (*cm/sec*)	1624.5 ± 295.5
Median of Homa – IR (%)	2.87 (0.74 – 10.21)
Median of Homa – β (%)	36.56 (3.51 – 355.50)

TABLE 2:

Distribution of subjects according to study completion

Study completion	n	%
Completed study	35	87.5
Stop due to SAE	1	2.5
Lost to follow up	4	10
Total	40	100.0

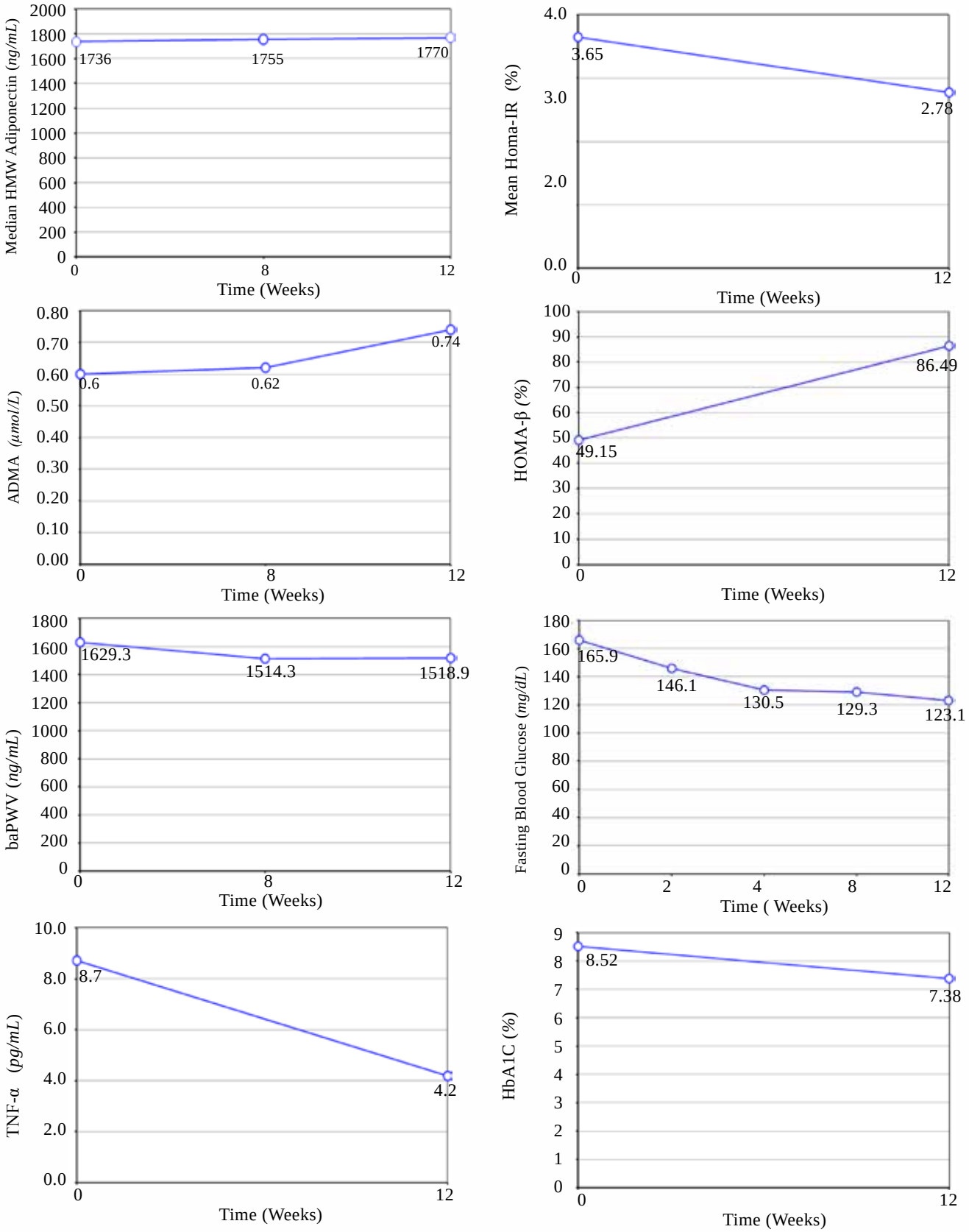

Figure 1: *Median changes of plazma HMW (A) adiponectin, ADMA (B), baPWV (C), TNF-α (D), Homa-IR (E), Homa-β (F), fasting blood glucose (G), HbA1C (H) according to visit.*
Notes: *HMW - high molecular weight, ADMA - asymmetric dimethylarginine, baPWV - brachial-ankle pulse wave velocity, TNF-α - Tumor necrosis factor alfa, HOMA-IR - homeostatic model assessment for insulin resistence, HOMA-β - Homeostatic model assessment for β-cell function, HbA1c - Hemoglobin A1c*

DISCUSSION

As Indonesia is entering the epidemiological transition period, many non-communicable diseases have recently showed significant increases. The latest Household survey reported that the incidence of diabetes in Indonesia, as one of the chronic degenerative diseases has increased. This study has recruited 40 patients of type-2 diabetes who have not been prescribed any OAD agents.

Diabetes Mellitus is defined as a group of metabolic diseases with characteristic of hyperglycemia due to abnormal insulin secretion or insulin action, or both [*American Diabetes Association., 2013*]. The prevalence of diabetes among Indonesian women is higher (6.4%) compared to men (4.9 %) [*Mihardja L et al., 2009*]. Studies in Japan showed the opposite distributions among female and male subjects [*Tsunekawa T et al., 2003; Nagasaka S et al., 2003*].

The prevalence of type 2 diabetes in Indonesia rises sharply in middle age (35-54 years) [*Mihardja et al., 2009*]. The mean of age in this study was 51.2 ± 5.1 years, which is similar to other study (Nagasaka 59 ± 2 years) [*Nagasaka S et al., 2003*]. Nakashima's study in Japan found older subjects with mean of 63.5 ± 1.1 years [*Nakashima R et al., 2006*].

The prevalence of diabetes gradually increases in line with the increasing body mass index (BMI). The BMI mean value in this study before treatment was 26.6 which decreased by 0.1 kg/m^2 after 12 weeks treatment with Glimepiride and Metformin fixed-dose combinations. Non-significant results were also found similar in the study by Tsunekawa T. [*Tsunekawa T et al., 2003; Nagasaka S et al., 2003*]. Different result was shown by Koshiba K. with a longer observation period for 28 weeks with a significant decrease in BMI by administering glimepiride or metformin monotherapy [*Koshiba K et al., 2006*].

This study showed decrease of mean *hba1c* levels, FBG levels and HOMA-IR. This study found an increase in the mean value of insulin and HOMA-β. Tsunekawa T. and Nagasaka S, also found similar results in their studies. This study found a mean decrease in *hba1c* level from 8.52 ± 0.9% to 7.38 ± 0.9% ($p<0.05$), in other studies, *hba1c* reduction showed 8.4 ± 1.9% to 6.5 ± 1.0% in Tsunekawa T. and 7.9 ± 0.2% to 7.1 ± 0.2% in Koshiba K. [*Tsunekawa T. et al., 2003; Kholili U et al., 2008*]. The results showed the main effects of both drugs. Glimepiride as insulin secretagogue increased insulin secretion from the pancreas, while metformin improves insulin sensitivity, and results in blood glucose lowering effect. In previous OAD monotherapy studies, either glimepiride or metformin showed similar *hba1c* reduction, between 1.0-2.0% [*Nathan DM et al., 2009*].

This study found a significant decrease in fasting glucose (153.5 to 112.0*mg/dL*), with similar extent reduction in Tsunekawa T., (157 ± 50 to 110 ± 39 *mg/dL*) and Nagasaka S (166 ± 7 to 147 ± 7 *mg/dL*) studies [*Tsunekawa T et al., 2003; Koshiba K et al., 2006*]. The results showed that Glimepiride and Metformin fixed dose combination may reduce blood glucose level significantly.

Currently there are several methods used to assess insulin resistance and pancreatic β cell dysfunction. The level of HOMA-IR of more than 4.0 indicates an insulin resistance and HOMA-β less than 70% indicates β cell dysfunction [*Tjokroprawiro A, 2008*]. This study showed a reduction of HOMA-IR from 3.66 ± 2.33 to 2.79 ± 1.7 ($p < 0.05$) while HOMA-β increased from 35.1% to 54.0%. Similar results were also obtained by Tsunekawa T. (HOMA-IR 2.54 ± 2.25 to 1.49 ± 0.71 and HOMA- β 35 ± 31% to 53 ± 35%) and Koshiba K. (HOMA-IR 2.41 ± 2.9 to 1.88 ± 1.1) [*Tsunekawa T et al., 2003, Koshiba K et al., 2006*].

Insulin is known to suppress the expression and secretion of adiponectin both in the in vitro and in vivo studies. Plasma insulin reduction caused by glimepiride may increase the concentration of circulating adiponectin, thus reducing the risk of onset and progression of blood vessels disease [*Tsunekawa T et al., 2003*]. Nevertheless, the decline in insulin level indicates severe dysfunction of beta cell. Based on the above results, both glimepiride or metformin monotherapy may improve insulin resistance characterized by a decrease in HOMA-IR level. However, the result of glimepiride on the improvement of pancreatic beta cells characterized by increased HOMA- β value are still varies.

Glimepiride has milder effect on insulin secretion, so it does not cause hyperinsulinemia. This study found a small insulin increase from 9.08 ± 5.0 *μU/dl* to 9.42 ± 5.9 *μU/dl*. Previous studies showed decreased insulin levels (6.5 ± 4.6 to 5.5 ± 2.0 *μU/dl*). Nagasaka also showed that fasting insulin level decreased significantly in the glimepiride group (11.7 ± 1.5 to 9.4 ± 1.0 *μU/ml* ,

p=0.007), whereas the increase in the metformin group was not significant (12.4 ± 2.0 to 13.8 ± 4.3 *μU/ml*, p=0.689) [*Nagasaka S et al., 2003*]. All results data demonstrated that the changes in fasting insulin levels by administration of Glimepiride and Metformin varied.

Various studies have shown that low level of adiponectin is associated with type 2 diabetes, obesity, insulin resistance, metabolic syndromes, dyslipidemia, cardiovascular diseases, hypertension, male sex hormones, oxidative stress, rich carbohydrates diet and related to genetic variation [*Kadowaki T et al., 2006*]. Adiponectin gene expression is controlled by metabolic stress conditions, several hormones and factors involved in the regulation of metabolic function. Insulin lowers adiponectin expression in mice and humans. Thiazolidinedione, a PPARγ (Peroxisome Proliferator Activated Receptor) agonist is a very potent drug in increasing the expression of adiponectin. Other factors that impact the regulation of adiponectin through inhibition effect are catecholamines, glucocorticoids, cytokines, prolactin, growth hormone and androgen [*Han SH et al., 2007*].

Based on epidemiological observations, decreased adiponectin levels can be prevented by treatments that can increase level of adiponectin. Therapeutic intervention to increase adiponectin level could be done by giving PPAR-γ agonists and provision of hypoglycemic drugs [*Han SH et al., 2007*]. Glimepiride has been reported to act as an activator of PPAR-γ [*Mather KJ et al., 2008*]. The effect of glimepiride in direct activation of PPAR-γ is equal to 16-25 % of maximum levels showed by thiazolidindione [*Fukuen S et al., 2005*]

This study found no significant difference between mean HMW adiponectin levels before and after administration of a fixed dose combination of Glimepiride and Metformin for 12 weeks (p>0,05). HMW adiponectin after treatment increased by 34.0 *ng/mL* from 1736.0 (293-6673) to 1770.0 (355-7207) *ng/mL*. It is assumed that the finding was due to the confounding variables that could not be controlled during the process of sample selection. These variables consist of genetic factors, BMI, gender, dyslipidemia, length of diabetes onset, and hypertension.

Contrary, Nagasaka and Tsunekawa T. found an increase in adiponectin levels after administration of glimepiride for 12 weeks with a value of 6.61 ± 3.06 *ug/ml* to 10.2 ± 7.14 *ug/ml* [*Tsunekawa T et al., 2003*] and a value from 22.1 ± 2.7 to 28.5 ± 2.8 *ug/ml* [*Nagasaka S et al., 2003*]. Koshiba K. with a longer observation time (28 weeks), found an increase in adiponectin level significantly after administration of glimepiride from 8.56 *ug/ml* to 15.26 mg/ml [*Koshiba K et al., 2006*].

Differences between this study compared to previous studies may be due to several factors including: the value of BMI, HOMA-IR, *hba1c*, high fasting glucose. In Tsunekawa T. study, the average values of BMI and HOMA-IR were lower than this study (21.2 ± 2.2 kg/m^2 and 2.54 ± 2.25 respectively). Koshiba K. study has values of 24.2 ± 2.2 BMI and HOMA-IR 1.88 ± 1.11. Existing research data indicated that high BMI is associated with the insulin resistance syndrome. Decrease in plasma adiponectin level can be associated with increased insulin resistance [*Nagasaka S et al., 2003; Tsunekawa T et al., 2003*].

Tsunekawa T. found a significant reduction of hba1c after glimepride administration for 12 weeks, from 8.4 ± 1.9% to 6.5 ± 1.0%. The subject were also given acarbose therapy (α-glucosidase inhibitor) 300 mg/day in addition to glimepiride, so the glycaemia control is better compared to this study. Subjects of the Tsunekawa T. study have higher initial adiponectin level due to the fact that they have consumed glibenclamide that activates PPARγ [*Fukuen S et al., 2005, Scarsi et al., 2007*]. Similar findings were reported by Koshiba K. subjects that consumed glibenclamide and have a longer observation period of 28 weeks [*Koshiba K et al., 2006*].

Glimepiride improves lipid metabolism and endothelial function through biosynthesis of nitric monoxide and its antioxidant effect; hence, it has antiatherosclerotic effect [*Davis SN, 2004*]. Several studies have shown that the biochemical parameters (IL-6, hs-CRP) were significantly decreased and pulse wave velocity parameter (baPWV, AI) also decreased after administration of glimepiride [*Koshiba K. et al., 2006*]. Metformin could prevent the damage to endothelial tissue under hyperglycemia condition. This effect is obtained not only because of the antihyperglycaemia pharmacological nature, but also due to the inhibition effects of the vascular endothelial cell damage [*Detaille D et al., 2005*].

This study showed significant decrease in vascular stiffness through measurement of baPWV (p<0.05) after administration of Glimepiride and

Metformin fixed-dose combination. Similar results were also obtained in the studies of Koshiba K. with the declining ba-PWV, accompanied by improved control of glucose and lipids as well as HOMA-IR decrease. One Japanese study comparing glimepiride, glibenclamide, and insulin for 28 weeks in 46 patients with type 2 diabetes, showed a significant difference of ba-PWV in the group receiving glimepiride therapy ($p<0.05$), but in the other two groups did not differ significantly [*Koshiba K et al., 2006*].

In diabetes mellitus Nitric Oxide-mediated endothelial vasodilation could be disrupted by hyperglycemia and insulin resistance. Hyperglycemia inhibits NO production by blocking the synthesis and activation of eNOS and increases reactive oxygen species. Insulin resistance results in activation of protein kinase C signaling enzymes, phosphatidyl inositol-3 (PI-3) kinase (eNOS agonist pathway) inhibition, and increase in ROS; a mechanism that directly interferes with the production of NO [*Chan J, Davidson J, 2007*]. Glimepiride resulted in improves lipid metabolism, and endothelial function due to nitric monoxide synthesis and has anti-oxidative effect and anti-atherosclerotic effect [*Koshiba K et al., 2006*]. Metformin has been known to have a protective effect on blood vessels, not solely due to the effect of glycemic improvement process. Some of the existing researches suggested that metformin may improve endothelial function, homeostasis, vascular inflammation, oxidative stress and improvement of microcirculation function that protect blood vessels [*Chan J, Davidson J, 2007*]. Glimepiride and Metformin combination therapy in this study has been shown to improve vascular stiffness as measured with baPWV.

Fixed dose combination glimepiride/metformin is proven effective to treat type 2 diabetes patients even though plasma adiponectin was not significantly increased by the administration of fixed dose combination glimepiride/metformin for 12 week treatment period among patients with type 2 diabetes as expected. However the treatment using fixed dose combination glimepiride/metformin could prevent progressive decreasing trend of adiponectin level. The level of adiponectin prior to the treatment was significantly affecting treatment response of type 2 diabetes patients. This study did not control important confounding factors of adiponectin and this fact has contributed to the result of the treatment in terms of the changes of adiponectin. Glimepiride has shown good treatment effect in increasing adiponectin only among subjects who have adiponectin dysfunction.

ADMA was significantly increased, while FBG and hba1c were significantly decreased following the treatment of fixed dose combination glimepiride/metformin. Brachial-ankle pulse wave velocity and HOMA-IR were significantly decreased, while HOMA-β showed an increase.

One subject developed thrombotic infarction that was diagnosed at the 8th week of visit and afterwards was hospitalized for 14 days. The subject consequently dropped out from this study although this serious adverse event was not related to the studied drug. The patient then recovered from the infarction with sequel. Risk factors of thrombotic infarction in this patient were type 2 DM with uncompliance treatment, hypertension with current therapy amlodipine 10 *mg* daily, dyslipidemia and high baPWV value (2200 *cm/sec*).

Atherothrombotic infarction occurs together with atherosclerosis. The degree of elevation of baPWV may correspond to the degree of atherosclerotic change: a very high baPWV may indicate that the atherosclerotic process was already well established. In Ogawa's study showed that there is an association between symptomatic cerebral infarction and high baPWV value in patients with type 2 diabetes. Increase patients branchial-ankle pulse wave velocity was found to be significantly higher than in patients without cerebral infarction (18.94 ± 4.95 versus 16.46 ± 3.62 *m/sec*) [*Ogawa O et al., 2003*].

Before switching to fixed dose combination glimepiride/metformin, 22 of 40 subjects (55%) were not rely on OAD, around 42.5% subjects used sulphonylurea as their main OAD and 2.5% subjects used. It can be concluded that treatment with fixed dose combination glimepiride/metformin has effect in improving endothelial function by increasing adiponectin and lowering baPWV level significantly. Meanwhile, the administration of fixed dose combination glimepiride/metformin may not have effect in decreasing ADMA level. Selection bias may have been introduced into our analysis due to 22 of 40 subjects (55%) were not relied on OAD, as we included patients who were not currently treated with any OAD. Further studies which included larger population with more varied parameters are needed to confirm the relationship of this fixed-dose combination with other factors.

REFERENCES

1. *American Diabetes Association.* Diagnosis and classification of diabetes mellitus. Diabetes care. *2013;* 36(1): S67-S74.
2. *Asagami T, Abbasi F, Stuelinger M, Lamendola C, Mclaughlin T., et al.* Metformin treatment lowers asymmetric dimethylarginine concentrations in patients with type 2 Diabetes. Metabolism. 2002; 51: 843-846.
3. *Baik S.* Comparison of the efficacy and safety of fixed-dose versus free combination of Glimepiride and Metformin in patients with type 2 Diabetes in Korea. J Med Ass Thai. 2005; 88: 245.
4. *Chan J, Davidson J.* Mechanisms of vascular protection with Metformin. In: Bailey, C. (Ed.) Metformin The Gold Standard. 1st Ed. 272. United Kingdom: John Wiley & Sons Ltd. 2007.
5. *Chan NN, Chan JC.* Asymmetric dimethylarginine (Adma): A potential link between endothelial dysfunction and cardiovascular diseases in insulin resistance syndrome? Diabetologia. 2002; 45: 1609-1616.
6. *Correia S, Carvalho C, Santos MS, Seica R, Oliveira CR, Moreira PI.* Mechanisms of action of metformin in type 2 Diabetes and associated complications: An overview. Mini Rev Med Chem. 2008; 8: 1343-1354.
7. *Davis SN.* The role of glimepiride in the effective management of type 2 Diabetes. J Diabetes Complications. 2004; 18: 367-376.
8. *Detaille D, Guigas B, Chauvin C, Batandier C, Fontaine E., et al.* Metformin prevents high-glucose-induced endothelial cell death through a mitochondrial permeability transition-dependent process. Diabetes. 2005; 54(7): 2179-2187.
9. *Fukuen S, Iwaki M, Yasui A, Makishima M, Matsuda M, Shimomura I.* Sulfonylurea agents exhibit peroxisome proliferator-activated receptor gamma agonistic activity. J Biol Chem. 2005; 280: 23653-23659.
10. *Gottsater A, Szelag B, Kangro M, Wroblewski M, Sundkvist G.* Plasma Adiponectin and serum advanced glycated end-products increase and plasma lipid concentrations decrease with increasing duration of type 2 Diabetes. Eur J Endocrinol. 2004; 151: 361-366.
11. *Han SH, Quon MJ, Kim JA, Koh KK.* Adiponectin and cardiovascular disease: response to therapeutic interventions. J Am Coll Cardiol. 2007; 49: 531-538.
12. *Hotta K, Funahashi T, Arita Y, Takahashi M, Matsuda M, Okamoto Y., et al.* Plasma concentrations of a novel, adipose-specific protein, Adiponectin, in type 2 diabetic patients. Arterioscler Thromb Vasc Biol. 2000; 20: 1595-1599.
13. *Imanishi R, Seto S, Toda G, Yoshida M, Ohtsuru A., et al.* High Brachial-ankle pulse wave velocity is an independent predictor of the presence of coronary artery disease in men. Hypertens Res. 2004; 27: 71-87.
14. *Kadowaki T, Yamauchi T, Kubota N, Hara K, Ueki K, Tobe K.* Adiponectin and Adiponectin receptors in insulin resistance, Diabetes, and the metabolic syndrome. J Clin Invest. 2006; 116: 1784-1792.
15. *Koshiba K, Nomura M, Nakaya Y, Ito S.* Efficacy of glimepiride on insulin resistance, adipocytokines, and atherosclerosis. J Med Invest. 2006; 53: 87-94.
16. *Lajer M, Tarnow L, Jorsal A, Teerlink T, Parving HH, Rossing P.* Plasma concentration of asymmetric dimethylarginine (Adma) predicts cardiovascular morbidity and mortality in type 1 diabetic patients with diabetic nephropathy. Diabetes Care. 2008; 31: 747-752.
17. *Liu H, Yambe T, Zhang X, Saijo Y, Shiraishi Y., et al.* Comparison of brachial-ankle pulse wave velocity in Japanese and Russians. Tohoku J Exp Med. 2005; 207: 263-270.
18. *Mather KJ, Funahashi T, Matsuzawa Y, Edelstein S, Bray GA., et al.* Adiponectin, change in adiponectin, and progression to diabetes in the diabetes prevention program. Diabetes. 2008; 57: 980-986.
19. *Meguro T, Nagatomo Y, Nagae A, Seki C, Kondou N., et al.* Elevated arterial stiffness evalu-

ated by brachial-ankle pulse wave velocity is deleterious for the prognosis of patients with heart failure. Circ J. 2009; 73: 673-680.

20. *Meguro T, Nagatomo Y, Nagae A, Seki C, Kondou N., et al.* Elevated arterial stiffness evaluated by brachial-ankle pulse wave velocity is deleterious for the prognosis of patients with heart failure. Circ J. 2009; 73: 673-680.
21. *Mihardja L, Delima Manz HS, Ghani L, Soegondo S.* Prevalence and determinants of diabetes mellitus and impaired glucose tolerance in Indonesia (A part of Basic Health Research/RISKESDAS). Acta Med Indones. 2009; 41: 169-174.
22. *Nagasaka S, Taniguchi A, Aiso Y, Yatagai T, Nakamura T., et al.* effect of glimepiride on serum adiponectin level in subjects with type 2 diabetes. Diabetes Care. 2003; 26: 2215-2216.
23. *Nakashima R, Kamei N, Yamane K, Nakanishi S, Nakashima A, Kohno N.* Decreased total and high molecular weight adiponectin are independent risk factors for the development of type 2 diabetes in Japanese-Americans. J Clin Endocrinol Metab. 2006; 91: 3873-3877.
24. *Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR., et al.* Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: A consensus statement of the American Diabetes Association and The European Association for the Study of Diabetes. Diabetes Care. 2009; 32: 193-203.
25. *Nathan DM.* Initial management of glycemia in type 2 diabetes mellitus. New England Journal of Medicine. 2002; 347: 1342-1349.
26. *Ogawa O, Onuma T, Kubo S, Mitsuhashi N, Muramatsu C, Kawamori R.* Brachial-ankle pulse wave velocity and symptomatic cerebral infarction in patients with type 2 Diabetes: a cross-sectional study. Cardiovasc Diabetol. 2003; 2: 10.
27. *Scarsi M, Podvinec M, Roth A, Hug H, Kersten S., et al.* Sulfonylureas and glinides exhibit peroxisome proliferator-activated receptor gamma activity: A Combined virtual screening and biological assay approach. Mol Pharmacol. 2007; 71: 398-406.
28. *Tjokroprawiro A.* Review article and clinical experience: Astaxanthin-oxidative stress-diabetes mellitus from basics to clinics and from general to specific. Folia Med Ind. 2008; 44: 293-299.
29. *Tsunekawa T, Hayashi T, Suzuki Y, Matsui-Hirai H, Kano H., 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.
30. *Wang CP, Hung WC, Yu TH, Hsu HL, Chen YH., et al.* Brachial-ankle pulse wave velocity as an early indicator of left ventricular diastolic function among hypertensive subjects. Clin Exp Hypertens. 2009; 31: 31-43.
31. *Yu K.* Pharmacokinetic profile of a new fixed-dose combination of glimepiride and metformin in healthy volunteers in Korea. J Med Ass Thai. 2005; 88: 241.