# DAMANHOUR UNIVERSITY
# FACULTY OF PHARMACY

**The effect of adding Vildagliptin versus Glimepiride to Metformin on markers of inflammation, thrombosis, and atherosclerosis in diabetic patients with symptomatic Coronary Artery Diseases.**

## Department of Post Graduate Studies and Research

# 2018/9/1

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# Scientific Protocol for (M.Sc.) Thesis in

# Pharmaceutical Science

# (Clinical Pharmacy)

In partial Fulfilment of the
Requirements for the Degree of
## (Master)
## By

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Title of the thesis

**The effect of adding Vildagliptin versus Glimepiride to Metformin on markers of inflammation, thrombosis, and atherosclerosis in diabetic patients with symptomatic Coronary Artery Diseases.**

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# Abstract

Diabetes mellitus is a chronic disease associated with a two- to fourfold increased risk of coronary artery diseases (CAD).(1, 2) Diabetes induces complex vascular changes, promoting accelerated atherosclerosis and hypercoagulability, as can be assessed indirectly by a number of markers. Principal perturbations include endothelial dysfunction, increased inflammatory plaque infiltration, adhesion molecule over-expression, adverse effects of circulating fatty acids and advanced glycosylation end products.

Vildagliptin, a potent and selective inhibitor of dipeptidyl peptidase-4 (DPP-4), improves glycemic control by increasing the availability of endogenous incretin hormones, glucagon- like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) (3). Complementing the pharmacological effect of metformin, vildagliptin enhances glucose-dependent insulin secretion and suppresses glucagon release, thereby improving glycemic control, and contributing to weight- neutrality and reduced hypoglycaemia(4) . Vildagliptin has demonstrated similar efficacy as an add-on to metformin when compared to SU with markedly reduced hypoglycaemia risk and no weight gain (5).

 Animal studies have suggested numerous beneficial anti-atherosclerotic changes of dipeptidyl peptidase-4 inhibitors (DPP4i), well beyond the effects on blood glucose alone (6, 7). Additionally, anti-remodeling effects are proposed (8). However, this feature has not been established in a clinical setting. Reduction of inflammatory marker levels is of great clinical importance and has been shown to correlate with reduction in significant clinical events (1, 9).

IL-1 is the pro-inflammatory mediator in both acute and chronic inflammation(10). It plays a major role in the activation of innate immunity(11), induces the synthesis and expression of multiple secondary inflammatory mediators including IL-6, IL-18 and IL-33(12, 13), and is strongly associated with the development of atherosclerosis and impairment of cardiac function in diabetic patients(14).

High sensitivity C-reactive protein (hs-CRP) is a marker of inflammation with a strong correlation with cardiovascular events even in normo-lipemic population (15). Reduction of hs-CRP has been demonstrated with vildagliptin-pioglitazone combination, but data from patients with symptomatic CAD and vildagliptin-metformin combination are lacking (16).

Adiponectin is a hormone with regulatory metabolic function secreted from the adipose tissue. Reduced levels of adiponectin were shown to be associated with obesity, metabolic syndrome, and diabetes, and to promote the atherosclerotic process (17, 18). Higher levels have been found to be protective (19). Reduction in adiponectin levels induced by fatty diet has recently been shown to be corrected by DPP4i in mice (6), yet the effect in diabetic humans is unknown.

Atherogenic index (AI) (LDL-C/ HDL-C) and coronary risk index (CRI) (TC/HDL-C) can be strong markers for predicting the risk of atherosclerosis and coronary heart disease and disclose the presence of LDL or TAG in the serum of related patients(20). Therefore, in the present study we plan to focus on possible anti-inflammatory and atherothrombotic protective effects of vildagliptin in a clinical setting.

# Research Objectives

The aim of this study is to evaluate the effect of adding Vildagliptin versus Glimepiride to Metformin on markers of inflammation, thrombosis, and atherosclerosis in diabetic patients with symptomatic CAD.

# Method & Proposal Steps

1- Approval will be obtained from Research Ethics Committee of Faculty of Pharmacy, Damanhour University.

2- All participants agreed to take part in this clinical study and provide informed consent.

3- Patients with CAD and uncontrolled DM type 2 who's taking metformin only will be enrolled (n=80) from endocrinology clinic at Alexandria Armed Forces hospital.

4- Complete physical, laboratory, radiological assessment will be done for all patients to exclude any signs of inflammation or thrombosis.

5- Serum samples will be collected for measuring the biomarkers.

6- All enrolled patients will be mentioned as two groups; Group I (n=40) are patients who the endocrinologist prescribed them vildagliptin plus their metformin to control their blood sugar level. Group II (n=40) are patients who the endocrinologist prescribed them glimepiride plus their metformin.

7- All patients will be followed up during 3 months' period.

8- At the end of 3 months on the new regimen, steps 4 and 5 will be repeated.

9- Statistical tests appropriate to the study design will be conducted to evaluate the significance of the results.

10- Measuring outcome: The primary outcome is the change of serum levels of the measured inflammatory markers after 3 months.

11- Results, conclusion, discussion and recommendations will be given.

## Inclusion criteria

- Adult patients with Type II-diabetes mellitus on metformin who are planned to be managed with vildagliptin or glimepiride plus metformin at the time of inclusion.
- Symptomatic Coronary Artery Diseases. (>30 days).

## Exclusion criteria

- Hepatic impairment.
- Active malignancy.
- Planned surgical intervention.
- Any signs of hypersensitivity or contraindication to study drugs developed.
- Any patient with any signs of active infection or thrombosis at the time of assessment.
- Addition of any antidiabetic medications or insulin during follows up.
- Chronic inflammatory disease (i.e. inflammatory bowel disease, lupus, inflammatory arthritis, rheumatoid arthritis) or chronic infection (i.e. chronic diabetic foot infection).
- Pregnancy, lactation or child-bearing potential.

# Methodology

- Interleukin1 beta (IL-1ß) and Adiponectin will be determined by ELISA.
- Lipid profile.
- Atherogenic index (AI = LDL-C/HDL-C) and CRI (CRI = TC/HDL-C) will be calculated for all subjects.
- High sensitivity C-reactive protein (hs-CRP) will be measured.
- Hb A1C will be measured.

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