Study of the Role of Apelin and Visfatin in Diabetic patients with Coronary Artery Disease

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"دراسة دور الأبيلين و الفيزفاتين فى مرضى السكرمن النوع الثانى الذين يعانون من امراض الشرايين التاجية"

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1. Introduction and Aim the of Work

Diabetes mellitus (DM) is a chronic metabolic disorder that affects more than 150 million people annually and is expected to reach 430 million by the year 2030 increasing exponentially especially in the developing countries ***(Stumvoll el al., 2005).*** Diabetes is an important risk factor for the development of coronary artery disease (CAD) ***(Norhammar et al., 2004),*** where it has been estimated that 75% of the deaths in diabetic patients may be attributed to CAD ***(Enas et al., 2007).***

Many mechanisms explaining pathogenesis of vascular complications in diabetic patients have been proposed and examined. These include hyperglycemia-induced inflammation, resulting from up-regulation of proinflammatory cytokines ***(Houstis et al., 2006)***, vasoconstriction, resulting from up regulation of vasoconstrictor peptides and down regulation of essential vasodilators as nitric oxide (NO) ***(Apreta et al., 2011)*** and increased reactive oxygen species (ROS) ***(Hopkins et al., 2007)*** that results in oxidative stress and cell damage (micro and macrovascular tissue damage) ***(Giacco and Brownlee, 2000).*** All of these enhance the formation of atherosclerotic plaques associated with either high risk of rupture or prolonged ischemia **(*Inoguchi et al., 2003)*.** Finally, this will end up with the metabolic syndrome (MS) which constitutes an agglomeration of type 2 diabetes (T2D) dyslipidemia and CAD ***(Rosenson, 2005).***

Systemic inflammation has also been closely associated with DM ***(Dandona et al., 2004).*** Higher levels of inflammatory indices and adhesion molecules are detected in patients with DM and CAD as compared to controls ***(Schillinger el al., 2003).*** Among the numerous circulating inflammatory markers of the atherosclerotic process, C-reactive protein (CRP) has received

the greatest attention. Moreover, CRP has been shown to impair insulin signaling and was found to be associated with insulin resistance (IR), adiposity, and MS ***(Devaraj et al., 2009).***

As a mere storage of lipids, lately, adipose tissue (AT) was proved to be a source of cytokines, termed adipokines, with various functions. Apelin was first recognized for the role of apelin/apelin receptor in the regulation of the cardiovascular system ***(Cheng et al., 2007).***

The other adipokine of interest in this study is visfatin. Visfatin is an insulin-mimetic adipokine that was originally discovered as a growth factor for β lymphocyte precursors ***(Francisca et al., 2011).*** Moreover, visfatin was found to be elevated in T2D, which points to its role in DM pathogenesis ***(Revollo et al., 2007; El-Mesallamy et al., 2011c).*** Interestingly, it has also been implicated in plaque destabilization leading to carotid and coronary atherosclerosis by up-regulating vasoconstrictors and generation of superoxides followed by inactivation of vasodilators ***(Kadoglou et al., 2010).***

Moreover, apelin and visfatin circulating levels in T2D postmenopausal females with and without CAD have not been fully studied. Also, their correlation with T2D, obesity and CAD needs further elucidation.

Accordingly, our study was conducted to:

1. Elucidate the role of CRP, apelin and visfatin in obese/non-obese T2D postmenopausal females with or without macrovascular complications namely CAD, being compared to healthy age-matched control subjects.
2. Investigate the possible association of the mentioned adipokines with each other and with other T2D associated hyperglycemia, inflammation and dyslipidemia biochemical markers in an attempt to explain how these potential players interrelate in the pathogenesis of diabetic CAD complications.
3. As far as our knowledge to study the correlation between these three players has not been explored before this work, hence we will provide further insight into the complex process of CAD development in T2D.

بسم الله الرحمن الرحيم

قَالُوا۟ سُبْحَٰنَكَ لَا عِلْمَ لَنَآ إِلَّا مَا عَلَّمْتَنَآ ۖ إِنَّكَ أَنتَ ٱلْعَلِيمُ ٱلْحَكِيمُ ﴿٣٢﴾

صدق الله العظيم

سورة البقرة آية ٣٢

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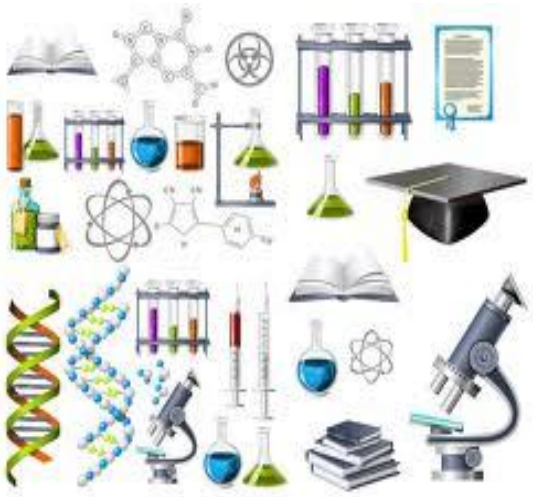
Subjects and Methods

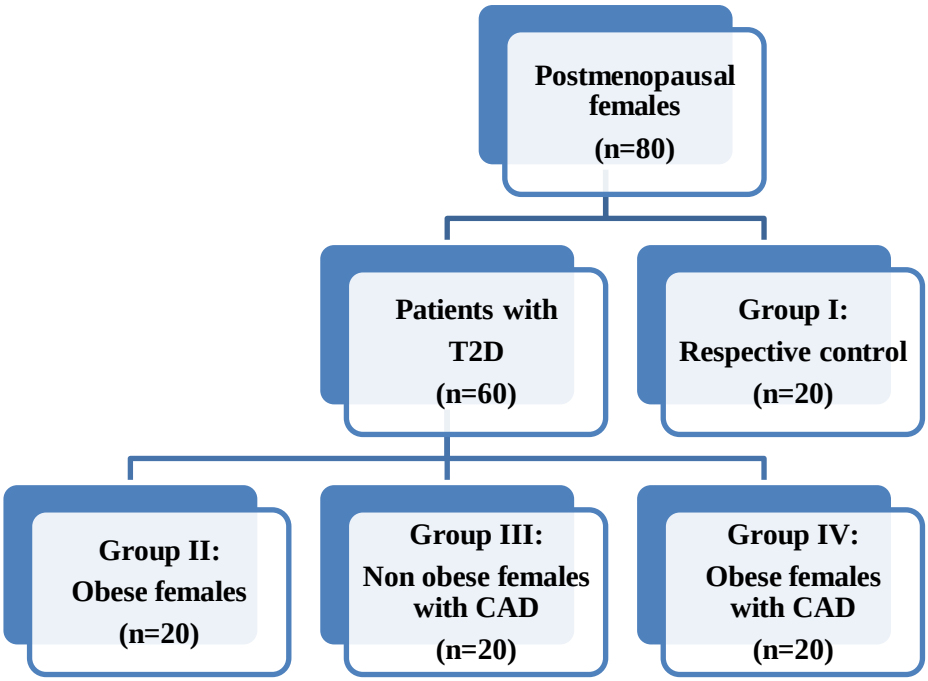


3. Subjects and Methods:

3.1) Subjects:

The study was approved by the Committees on Medical Ethics of Ain-Shams Specialized hospital. The study was carried out in accordance with the regulations and recommendations of Declaration of Helsinki, where all subjects gave written informed consent prior to participation.

The study population comprised 80 subjects classified into the following 4 groups as illustrated in the following diagram:



Group I: Composed of 20 healthy control postmenopausal females, working in, or attending with their relatives, to the Outpatient Clinics of Ain-Shams University Teaching Hospitals. Their mean age was 62.35±0.46 years; mean body mass index (BMI) was 26.10±0.21 (Kg/m^2). These females were not suffering from any health related problems nor were taking any medication or dietary supplements including vitamin(s) and/or antioxidant(s).

Group II: Comprised 20 obese postmenopausal females suffering from T2D attending the Outpatient Clinic of Ain-Shams University Teaching Hospitals. Their mean age was 63.40±0.53 years with mean duration of DM 13.45±0.5 years, and mean BMI was 35.16±0.63 (Kg/m^2).

Group III: This group included 20 non obese postmenopausal females suffering from T2D with CAD in the Intensive Care of the Cardiology Department of Ain-Shams University Teaching Hospitals. Their mean age was 63.35±0.54 with mean duration of DM 14.15±0.55 years, and mean BMI was 26.73±0.29 (Kg/m^2). Patients suffered from either: (n=10) angina, (n=5) ischemia, or (n=5) clots in the coronary arteries.

Group IV: Composed of 20 obese postmenopausal females suffering from T2D with CAD in the Intensive Care of the Cardiology Department of Ain-Shams University Teaching Hospitals. Their mean age was 64.70±0.45 years with mean duration of DM 13.95±0.54 years, and mean BMI was 37.66±0.40 (Kg/m^2). Patients were suffering from either: (n=9) angina, (n=6) ischemia, or (n=5) clots in the coronary arteries.

- **The following exclusion criteria were used for all study participants:**

All patients were free of chronic liver diseases, acute or chronic renal disease, hyperthyroidism, pituitary disorders, free from malignancy, autoimmune disease, and any acute or chronic inflammatory diseases. Patients were not taking any anti-inflammatory drugs, as well as other medications that may affect the heart. Patients were not suffering from type 1 DM (T1D) as well. Any patient receiving insulin injections was excluded from the study.