

# Serum Fetuin-A, A New Potential Biomarker For Diagnosis Of IHD In Menopausal Women.

استخدام فيتوين أ (Fetuin-A) كمؤشر حيوي لتشخيص مرض القلب الأقفاري لدى النساء في سن اليأس.

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## الخلاصة:

**المقدمة:** دراسة المؤشرات الحيوية ومساراتها الكيميائية تسمح بتطور العديد من الاستراتيجيات الجديدة في تشخيص النساء المصابات بمرض القلب الأقفاري في سن اليأس. أحد هذه المؤشرات الحيوية هو (Fetuin-A).

**هدف الدراسة:** دراسة أهمية المؤشر الحيوي (Fetuin-A) في تشخيص مرض القلب الأقفاري لدى النساء في سن اليأس.  
**منهجية العمل:** شملت الدراسة ٧٦ من النساء المصابات بمرض القلب الأقفاري بالإضافة إلى ٢٠ من النساء الأصحاء. تم تقسيم المريضات إلى عدة مجاميع بناءً على وجود مرض السكري وارتفاع ضغط الدم ثم تم قياس مستوى (Fetuin-A) في الدم لدى كافة النساء.

**النتائج:** أظهرت الدراسة انخفاض معنوي في مستوى (Fetuin-A) في الدم لدى النساء المصابات بمرض القلب الأقفاري.

**الاستنتاج:** يمكن استخدام (Fetuin-A) كمؤشر حيوي لتشخيص المصابات بمرض القلب الأقفاري.

**التوصيات:** دراسة المؤشر الحيوي (Fetuin-A) في تشخيص مرض القلب الأقفاري لدى الرجال والنساء وفي أعمار مختلفة.

## Abstract

**Background:** The role of inflammation in atherogenesis would suggest, a great deal of work looking for inflammatory markers that are risk factors for IHD. The most extensively examined markers are fibrinogen, C-reactive protein, IL-6, homocysteine, and fetuin-A.

**Aim of the study:** The present study is focusing on role of biomarker fetuin-A in the diagnosis of IHD in menopausal female.

**Method:** This study involved 76 menopause women suffering from IHD (42 patients with AMI and 34 with angina) and 20 healthy menopause women as control. Patients were divided into subgroups according to the presence of DM and hypertension. Serum Fetuin-A level is estimated in each group.

**Results:** There is significant reduction in serum fetuin-A levels in menopausal women with IHD. Diabetes mellitus and hypertension associated with significant decrease in serum fetuin-A levels in menopausal women with IHD.

**Conclusion:** Serum fetuin-A can be used as biomarker for diagnosis of angina and AMI in menopausal women. Both DM and hypertension have detrimental effect on serum fetuin-A levels.

**Key words:** Fetuin-A, IHD, DM, menopause.

## INTRODUCTION

Menopause is best defined as the absence of menses for twelve consecutive months. It is a physiologic phase of a woman's life, result from loss of ovarian function with subsequent deficiency of estrogen hormone. The incidence and prevalence of IHD are higher in menopausal women; hence, various available and prospective markers in relation to menopausal IHD risk were analyzed<sup>(1)</sup>. Women account for 52% of all deaths due to heart diseases, among the female patients who die suddenly from coronary heart attacks, 64% have had no previous symptoms<sup>(2)</sup>. The role of the natural menopause on cardiovascular disease is unclear. Several studies have reported adverse effects of the menopause on cardiovascular risk factors such as lipid profiles, blood pressure, reduced glucose tolerance, obesity, endothelial dysfunction, and vascular inflammation. However, it is difficult to distinguish a discrete effect of the menopause on cardiovascular risk from age-related effects<sup>(3, 4)</sup>.

Coronary heart disease (also known as coronary artery disease or ischemic heart disease) is the most common form of heart disease and results from atherosclerosis<sup>(5)</sup>. Atherosclerosis is a disease characterized by the formation of thickenings of the innermost layer of the arterial wall. These thickenings or atherosclerotic plaques develop in large and medium-sized arteries preferentially at sites with turbulent flow, typical of bifurcations, and curvatures. Atherosclerotic lesions are characterized by inflammation, lipid accumulation, cell death, and fibrosis. Clinical complications of atherosclerosis may arise from flow-limiting stenosis, but most of the fatal clinical events are caused by the rupture of a plaque<sup>(6)</sup>. Current major IHD risk factors are male sex, increasing age, family history, smoking habit, presence of diabetes, obesity (especially high levels of visceral adiposity), hypertension, hyperlipidemia and a sedentary lifestyle. Most of these risk factors interrelate in some way either directly or indirectly<sup>(7, 8)</sup>. Some haemostatic markers have also shown association with incident IHD, perhaps due to their roles in thrombus formation, longevity, and degradation. These include fibrin D-dimer fragment<sup>(9)</sup>, von Willebrand factor vWF<sup>(10)</sup>, and tissue plasminogen activator t-PA<sup>(11)</sup>. The role of inflammation in atherogenesis would suggest, a great deal of work looking for inflammatory markers that are risk factors for IHD<sup>(12)</sup>. The most extensively examined markers are fibrinogen, C-reactive protein (CRP), white cell count (WCC), IL-6, homocysteine, and fetuin-A<sup>(13, 14)</sup>. Some of these biomarkers can enhance plaque formation such as CRP that is considered as positive acute phase protein mediated LDL uptake by macrophage, which lead to the formation of foam cells; while, fetuin-A is negative acute phase protein that enhances vascular calcification and lead to plaque formation<sup>(15)</sup>.

Fetuin-A ( $\alpha$ 2-Heremans Schmid glycoprotein AHSG) is a circulating glycoprotein synthesized mainly by the liver. It is a member of the cystatin super-family of cysteine protease inhibitors<sup>(16)</sup>. Fetuin-A, which is down-regulated in response to inflammation, is known to be a negative acute phase reactant. It can inhibit insulin receptor tyrosine kinase activity, resulting in insulin resistance<sup>(17)</sup>. Besides that, fetuin-A has been recognized as a potent calcification inhibitor<sup>(18)</sup>. Fetuin-A is a major inhibitor of vascular calcification and serum concentrations of fetuin-A are depressed in patients with ESRD. Due to its high affinity for calcium phosphates, fetuin-A accumulates in the atherosclerotic plaques, and in pathologically mineralized tissues<sup>(19)</sup>.

## **OBJECTIVE OF THE STUDY:**

The present study is focusing on role of biomarker fetuin-A in the diagnosis of IHD in menopausal female.

## **PATIENTS AND METHODS**

This is a case control study involved seventy six menopause women, diagnosed by history of amenorrhea for at least twelve months, aged 50-70 years ( $58 \pm 6.3$  yr), with clinical evidence of IHD in form of angina (34 patients) or acute myocardial infarction (AMI) (42 patients). Diagnosis of angina and myocardial infarction was based on typical chest pain, positive ECG change, and positive cardiac markers estimation. The patients were collected from the coronary care unit (CCU) in Al-Sadder Teaching Hospital, in Al-Najaf Al-Ashraf, during the period from January to August 2012.

Menopausal women with angina were further classified in to women with DM (16 patients), women without DM (18 patients), hypertensive women (15 patients)

and normotensive women (19 patients). Menopausal women with AMI were also classified into diabetics (23 patients), non-diabetics (19 patients), hypertensive (20 patients), and normotensive (22 patients). The study also involved twenty menopause women, without evidence of IHD, aged 49- 65 years ( $55 \pm 4.5$ yr), as control group. Both patients and control women are informed about the study and consent is ensured. All participants are exposed to questionnaire about age, chest pain, history of admission to CCU, smoking, history of hypertension and diabetes mellitus, and drug history. Blood samples were drawn by trained nurses within 24 hours from admission, and sent for baseline investigations, as well as samples of sera were kept freezing at  $-20^{\circ}\text{C}$  for estimation of serum Fetuin-A. Exclusion criteria were smoking, history of estrogen therapy, evidence of renal or hepatic disease.

#### Estimation serum Fetuin-A

Estimation serum Fetuin-A, is carried out by specific kit for test, supplied by (usbiological-United States Biological.,co.USA-Catalog No. F4102-01).

#### Statistical analysis

Data are presented as the mean  $\pm$  standard error (SE). t-test was used for statistical analysis, p-value  $< 0.05$  was considered significant.

## RESULTS

**Table 1: Serum fetuin-A levels in menopausal women with IHD (AMI and angina) and healthy menopausal women.**

| Study group                              | Serum fetuin-A         |
|--|------------------------|
| Menopausal women with AMI<br>(n = 42)    | $26.53 \pm 1.08$ ng/ml |
| Menopausal women with angina<br>(n = 34) | $30.82 \pm 1.31$ ng/ml |
| Healthy menopausal women<br>(n = 20)     | $69.60 \pm 1.07$ ng/ml |

p-value  $< 0.05$

**Table 2: Serum fetuin-A levels in diabetic and non-diabetic menopausal women with (AMI and angina).**

| Study group                              | Diabetic Women                     | Non-diabetic women                   |
|--|------------------------------------|--------------------------------------|
| Menopausal women with AMI<br>(n = 42)    | $17.04 \pm 1.45$ ng/ml<br>(n = 23) | $26.72 \pm 1.05$ ng/ml<br>(n = 19)*  |
| Menopausal women with angina<br>(n = 34) | $23.23 \pm 0.91$ ng/ml<br>(n = 16) | $30.86 \pm 2.40$ ng/ml<br>(n = 18)** |

\*p-value  $< 0.05$  \*\* p-value  $< 0.05$

**Table 3: Serum fetuin-A levels in hypertensive and normotensive menopausal women with (AMI and angina).**

| Study group                  | Hypertensive women                 | Normotensive women                   |
|------------------------------|------------------------------------|--------------------------------------|
| Menopausal women with AMI    | $18.54 \pm 0.91$ ng/ml<br>(n = 20) | $26.80 \pm 1.33$ ng/ml<br>(n = 22)*  |
| Menopausal women with angina | $29.02 \pm 1.42$ ng/ml<br>(n = 15) | $37.15 \pm 1.99$ ng/ml<br>(n = 19)** |

\*p-value  $< 0.05$  \*\* p-value  $< 0.05$

There was significant decrease in serum fetuin-A levels in menopausal women with IHD (AMI and angina) compared to healthy menopausal women. Table 1.

Study of serum fetuin-A levels in relation to DM showed significant decrease in serum fetuin-A levels in diabetic menopausal women compared to non-diabetic menopausal women for both AMI and angina group. Table 2.

Study of serum fetuin-A levels in relation to hypertension, revealed significant decrease in serum fetuin-A levels in hypertensive menopausal women compared to normotensive menopausal women for both AMI and angina group. Table 3.

## DISCUSSION

In this study there was a significant decrease in serum fetuin A level in menopausal patients with IHD compared to healthy menopause, this result is agreed with Axel *et al*, who found that reduced fetuin-A levels has been associated with coronary atherosclerosis and increased cardiovascular mortality, suggest that Fetuin-A is a potent inhibitor of vascular calcium deposition and lower level associated with atherosclerosis expressed by the extent of coronary artery calcified plaque<sup>(20)</sup>. Ombrellino *et al.*, Christophe *et al.*; and Ruminy *et al.* stated that Fetuin-A is an anti-inflammatory mediator that participates in macrophage deactivation. Fetuin-A enhances the cellular uptake of cationic inhibitors of pro-inflammatory cytokine synthesis by macrophages and hence it prevents the morbid sequelae of infection and inflammation that would result from overproduction of pro-inflammatory cytokines. This event mainly result from an interleukin-1 $\beta$  (IL-1 $\beta$ ) induced down-regulation of its hepatic mRNA level<sup>(21, 22)</sup>. The present study showed significant association between low Fetuin-A levels and DM in menopausal women with IHD, this finding supports preliminary data by Peter *et al.* who found significant association between coronary calcifications and low fetuin-A levels in diabetic patients<sup>(23)</sup>.

In the current study there was significant association between low Fetuin-A levels and hypertension in menopausal women with IHD; Alqasim suggested that low level of the anti-calcification fetuin-A in hypertensive patients is a possible contributory factor for arterial stiffness<sup>(24)</sup>.

## CONCLUSIONS

Serum fetuin-A can be used as biomarker for diagnosis of angina and AMI in menopausal women. Both DM and hypertension have detrimental effect on serum fetuin-A levels.

## RECOMMENDATION

Study Serum fetuin-A levels in patients with IHD of different sex and in different age groups.

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