

ASSOCIATION BETWEEN CIRCULATING FETUIN-A LEVELS AND TYPE II DIABETES MELLITUS: A SYSTEMATIC REVIEW AND META-ANALYSIS OF OBSERVATIONAL STUDIES



Biochemistry

Rekha Choudhary Ph.D Scholar (Department Of Biochemistry) People's College Of Medical Sciences & Research (Bhopal) - Corresponding Author

Dr. P.J. Hisalkar Professor & Head (Department Of Biochemistry) People's College Of Medical Sciences & Research (Bhopal)

ABSTRACT

Introduction- Serum fetuin-A is a multifunctional glycoprotein which is exclusively secreted from hepatocytes in human. This study was conducted to determine the association between Fetuin-A and type 2 diabetes in different studies.

Material and Methods- literature search from different databases was done and Meta-Analysis was conducted using MOOSE guidelines. 14 full-text articles were selected among them 7 articles were used for quantitative synthesis. A total of 1011 diabetic patients were seen in the study out of 5056 participants. SPSS and Revman softwares were used for analysis.

Results- The concentration of fetuin A was found to be higher in diabetic patients. Forest plot showing combined results of seven observational studies, with three studies favouring control and four studies favours association between Fetuin-A with diabetics.

Conclusion- In conclusion, higher fetuin-A concentrations appear to be strongly associated with diabetes risk among both sexes, age (>40) years etc.

KEYWORDS:

Fetuin-A, diabetes, Meta-analysis.

Introduction-

In India, diabetes mellitus currently affects 7.8% of the population aged 30 years or older, with the prevalence being higher among males. One novel factor of interest is fetuin-A, a hepatic secretory protein found in high concentrations in human serum [1]. Serum fetuin-A (also called alpha-2 heremans schmid glycoprotein, AHSG) is a multifunctional glycoprotein which is exclusively secreted from hepatocytes in human [2]. For a long time, fetuin-A has been considered to play a crucial role in the protection from vascular calcification by solubilizing calcium and phosphorus in serum [3,4,5]. In vitro studies demonstrate that fetuin-A can noncompetitively and reversibly bind the insulin receptor tyrosine kinase in muscle and fat, inhibiting downstream internal signaling cascades and resulting in peripheral insulin resistance [3]. An association between higher circulating fetuin-A concentrations and incident diabetes has consistently been reported in several prospective epidemiologic studies [4,5,6,7,8]. It was also reported that fetuin-A could inhibit insulin receptor tyrosine kinase activity through blocking the autophosphorylation of tyrosine kinase and insulin receptor substrate-1 (IRS-1), and induced a lower-grade inflammation [6,7], which resulted in insulin resistance [8,9,10,11]. Recently, epidemiological studies showed that serum fetuin-A was associated with type 2 diabetes [12,13]. So the rationale behind the study was to investigate the association of serum fetuin-A with prediabetes and type 2 diabetes population aged 30 or above.

Material and Methods-

A systematic search of the PubMed, EMBASE, ISI Web of Knowledge, and Cochrane Library databases up until 24th April 2017 was conducted to retrieve observational studies matched to search terms like pre- diabetes, type 2 diabetes, Fetuin- A, association etc. We conducted the present meta-analysis in accordance with the guidelines of the Meta-analysis of Observation Studies in Epidemiology Group (MOOSE). We included only observational studies that reported original data relevant to measuring the increased risk for type 2 diabetes in pre diabetes patients associated with elevated levels of Fetuin-A. A total of 274 records were identified through database searching and additional sources, out of 274 records 200 were duplicate records which were excluded, among 74 articles, there were 14 full-text articles among them 7 articles were used for quantitative synthesis. A total of 1011 diabetic patients were seen in the study out of 5056 participants. A pre- tested semi-structured questionnaire was used to extract the following information from the published article for each included article: first author's name, publication year, sample size, study design, mean (SD) for Fetuin-A levels, geographic location of participants, mean age, outcome assessment, reported relative risks (RRs) or hazard ratios (HRs) of type 2 diabetes and the corresponding 95% CIs. Inclusion criteria for the studies only if the study design was observational studies or cross-sectional studies and those who were

diagnosed diabetic in the last 5 years were included in the study. Case-control, cohort studies, review article, studies of gestational diabetes or type 1 diabetes or animal studies were excluded. The full text and any supplementary materials were examined for data extraction. We also extracted the effect estimate. The summary risk estimates were pooled using either fixed-effects or random-effects models to incorporate between-study variation. The multivariable regression or odds ratios reported in the eligible studies were extracted and considered directly as RR in our analysis. RR was used to measure the relationship between Fetuin -A levels and the risk of type 2 diabetes in patients. Heterogeneity across studies was tested using the Cochrane Q test and the I² test. Data from the studies were combined using a fixed-effects model or a random-effects model. All statistical analyses and contour enhanced funnel plots were performed using SPSS (version 23) and Revman Software.

Results-

Table 1- Baseline characteristics of diabetic and subcohort participants among different studies

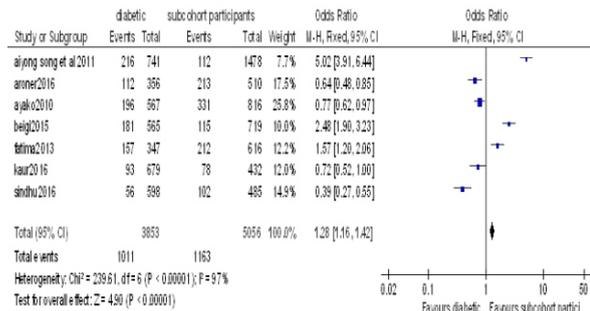
Variable	Diabetic (N=1011)		Subcohort participants (N=5056)	
	N	Mean (SD)	N	Mean (SD)
Fetuin-A(g/dl)	-	0.48(0.12)	-	0.42(0.10)
Age (years)	-	42.5(10)	-	43(12)
BMI	-	28.6(4.2)	-	26.2(3.6)
Family income >25000/month	786*	-	3746*	-
Alcohol (>1drink/week)	576*	-	2326*	-
Fasting plasma glucose	-	112(96-120)	-	88(82-96)
Waist circumference	-	106(14)	-	96(34)
Total cholesterol	-	188(34)	-	188(34)

*- multiple responses

Table 1 shows baseline characteristics of diabetic patients and other participants among different variables in different observational studies. The concentration of fetuin A was found to be higher in diabetic patients as compared to subcohort participants. The mean age is 42.5±10 years in diabetic patients. The BMI, waist circumference, fasting plasma glucose and total cholesterol all are higher in diabetic patients as compared to other participants in all the studies.

Figure 1 – forest plot showing combined results of seven observational studies, with three studies favouring control and four

studies favours association between Fetuin-A with diabetics. The size of the squares is proportional to the inverse of the variance of the ORs. The diamond represents the summary estimates. The combined risk ratio for diabetes comparing individuals in studies of baseline Fetuin-A distribution was 1.28 (95% CI 1.16-1.42), with substantial heterogeneity between studies ($I^2=97\%$, $p=0.0001$), as shown in Fig. 1.



Discussion-

In these multicentric observational studies of middle-aged to older adults without clinically evident cardiovascular disease at study inception, higher serum fetuin-A concentrations were strongly associated with risk of incident diabetes among females. People with pre diabetes in the highest fetuin A had a higher rate of progression to diabetes which approached statistical significance (RR 11.96, 95% CI 5.9-24.01, $p= 0.001$) and a significantly lower rate to reversion to normoglycemia (RR 5.62, 95% CI 3.16-9.6, $p=0.001$). In the EPIC postdam study [9] subjects with normoglycemia in the highest fetuin A quartile had a significantly higher risk of diabetes than those in the lowest quartile (RR 1.75, 95% CI 1.32-2.31 $p= 0.001$), similar results have been reported in another study. In nurses health study [13], fetuin A was a predictor of diabetes where with each 100 µg/ml rise in fetuin A was associated with a 27% higher risk of diabetes. Increase in fetuin A was observed to be independent of inheritance pattern i.e. whether mother or father was diabetic, but when both parents were diabetic the levels were much more as compared to when either parent was diabetic [14]. Fetuin A correlated positively with fasting plasma glucose and glycosylated Hb thereby suggesting that fetuin A can be a better marker of Insulin resistance instead of glycosylated Hb, as Glucose and glycosylated Hb are affected by a number of factors like Diet [15,16], Plasma Albumin content, Alcoholism, Hemoglobinopathies, Chronic Renal Failure and Hyperbilirubinemia [17]. In addition there was observed a significant positive correlation between fetuin A and insulin $r= +0.289$, $p<0.001$, fetuin A and c-peptide $r=+ 0.177$, $p<0.001$, fetuin A and %β cell function $r= -0.368$, $p<0.001$, Fetuin A and % sensitivity to insulin $r= -0.287$, $p<0.001$, fetuin A and insulin resistance $r= +0.436$, $p<0.001$). Further support for a potential role of fetuin A in regulation of glucose metabolism is its correlation with inheritance pattern as the gene encoding for fetuin A has been found to be located on chromosome 3q27, the region that was previously mapped as a susceptibility locus for metabolic syndrome [18] or insulin resistance. Thus the present study highlights the importance of fetuin A as a biomarker for assessing the status of an individual and an effective indicator of the diabetes.

Conclusion- In conclusion, higher fetuin-A concentrations appear to be strongly associated with diabetes risk among both sexes, age (>40) years, high BMI, high waist circumference. Associations of fetuin-A with diabetes were minimally attenuated after adjustment for subcohort participants these did not modify associations of fetuin-A with diabetes in either sex or other variables. Future studies are needed to clarify discrepancies in associations across studies and to investigate potential mechanisms through which fetuin-A might be related to the development of diabetes.

Conflict of interest- none declared

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