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RELATIONSHIP BETWEEN INFLAMMATORY MARKER (CRP) AND THE RISK OF TYPE II DIABETES MELLITUS IN PRE-DIABETIC PATIENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS.

Biochemistry

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ABSTRACT

Introduction- The prevalence of type 2 diabetes (T2DM) is increasing worldwide and exhibits a challenge on the health care system as well as on the public health. This Meta-analysis was done to determine relation between CRP and type 2 DM.

Material and Methods- We conducted the present meta-analysis in accordance with the (MOOSE) guidelines. Only prospective studies were included. Literature search was done using different databases. SPSS and Revman software were used for analysis.

Results- The concentration of CRP was found to be higher in diabetic patients as compared to non-diabetic participants. The combined risk ratio for diabetes comparing individuals in funnel plot, CRP distribution was 5.39 (95% CI 4.49-6.47), with substantial heterogeneity between studies.

Conclusion- The associations between CRP and type 2 diabetes appear to be stronger than previously reported, and that CRP may be an independent risk factor for type 2 diabetes.

KEYWORDS:

CRP. Diabetes, Meta-analysis.

Introduction -

The prevalence of type 2 diabetes (T2DM) is increasing worldwide and exhibits a challenge on the health care system as well as on the public health and socioeconomic development of all nations. The causes of T2DM are multifactorial and result from a combination of environmental and genetic risk factors. The implementation of preventive measures in populations and the identification of high risk groups, which mostly benefit from such activities, will be the key point for the early prevention of T2DM and its complications(1). Prediabetes is a condition in which individuals have blood glucose levels higher than normal but not high enough to be classified as diabetes, hence projected as a precursor to diabetes. It refers to a state of impaired glucose tolerance, or, impaired fasting glucose either singly or in combination. Pre-diabetes can be diagnosed by blood sugar test such as fasting plasma glucose (FPG) and oral glucose tolerance test (OGTT). The American Diabetes Association (ADA) criteria for diagnosis of pre diabetes based on expert committee recommendations (2) are as follows:

- FPG =100 - 125 mg/dl (5.6 - 6.9 mmol/l) = impaired fasting glucose (IFG)
- 2 h post load glucose = 140 - 199 mg/dl (7.8 - 11.1mmol/l) = impaired glucose tolerance (IGT)
- HbA1c of 5.7 - 6.4% (this has been recently added)

In this regard, more recent data suggest that interleukin-6 (IL-6) and C-reactive protein (CRP) are associated with type 2 diabetes (3,4,5) in prediabetes patients. CRP is an acute-phase plasma protein synthesized by the liver and has been shown to be a sensitive, systemic biomarker of inflammation (6). Two previous meta-analyses evaluating the association of CRP and diabetes risk have yielded contradictory results. The objective of the current study was to estimate the magnitude of the relationships between CRP levels and the risk of type 2 diabetes in pre diabetic patients and to quantify these relationships in a meta-analysis.

Material and Methods- A systematic search of the PubMed, EMBASE, ISI Web of Knowledge, and Cochrane Library databases up until 10 February 2017 was conducted to retrieve prospective studies matched to search terms like pre- diabetes, type 2 diabetes, IL-6, CRP, 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 prospective studies that reported original data relevant to measuring the increased risk for type 2 diabetes in pre diabetes patients associated with elevated levels of IL-6 and CRP. A pre- tested data collection form 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 IL-6 and CRP levels, geographic location of participants, mean age, race/ethnicity, duration of follow up, proportion of women, 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 a prospective cohort study, a case-cohort study, or a nested case-control study. In these studies, participants were excluded on the basis of having previously had diabetes recorded and a follow-up duration of 1 year. Cross sectional studies, literature reviews, 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. RR was used to measure the relationship between CRP levels and the risk of type 2 diabetes in pre diabetes patients. All statistical analyses and contour enhanced funnel plots were performed using SPSS. Literature search is done under following steps:

I. Identification- 179 records identified through database searching and 16 addtional records through other sources.
II. Screening- 112 duplicate records were removed, 67 records screened in which 57 records excluded.
III. Eligible- 10 full text articles are assessed for eligibility. 4 studies are excluded.
IV. Included- 6 studies included for quantitative analysis (META-ANALYSIS).

Results-

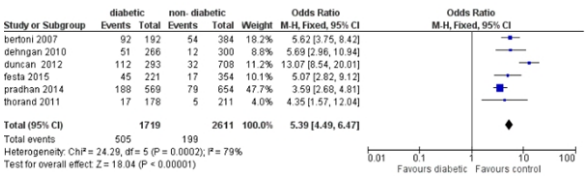
Table 1- Baseline characteristics of diabetic and non-diabetic participants among different studies

Variable	Diabetic (505)	Non-diabetic(2611)	p-value
	Mean (SD)	Mean (SD)	
CRP(mg/dl)	4.8±2	3.8±2	S
Age (years)	52.8±8.3	50.2±8	NS
BMI	29.4±4.4	26.6±3.8	S
HbA1c(%)	8.2±1.6	5.2±0.6	S
SBP	148±16.2	126±18.4	S
Fasting plasma glucose	112(96-120)	88(82-96)	S
Waist Hip Ratio	0.98±0.8	0.84±0.6	S
Male sex	310(61.4)	510(56.6)	S NS

NS- non-significant
S- Significant (P<0.05)

Table 1 shows baseline characteristics of diabetic patients and other participants among different variables prospective studies. The concentration of CRP was found to be higher in diabetic patients as compared to non-diabetic participants. The mean age is 52.5±8.3 years in diabetic patients. The BMI, waist hip ratio, fasting plasma glucose and SBP all are higher in diabetic patients and are significant as compared to other participants in all the studies.

Figure 1- Prospective studies of the association between CRP levels and type 2 diabetes. The size of the squares is proportional to the inverse of the variance of the ORs. The diamond represents the summary estimates.



Out of sixteen studies, six studies were included for meta-analysis depending upon the role of CRP on diabetic patients studies, comprising a total of 505 incident diabetes cases with raised CRP levels out of 1719 diabetic cases and 199 events in non-diabetic cases out of 2611were included in the meta-analysis. The combined risk ratio for diabetes comparing individuals in top vs bottom thirds of baseline CRP distribution was 5.39 (95% CI 4.49-6.47), with substantial heterogeneity between studies (I^2=79%,p=0.0002), as shown in Fig. 1.

Discussion-

The present metaanalysis of prospective studies suggests a significant association of elevated levels of IL-6 and CRP with type 2 diabetes risk. Our findings further support the hypothesis that chronic inflammation is a predictor of type 2 diabetes development. In subgroup analyses, the associations of CRP with diabetes were not substantially changed by geographic region. An association was demonstrable when only a restricted list of possible confounding factors was considered, but was entirely attenuated when WHR, SBP, HbA1c were considered, suggesting that these factors are important confounders. The possibility of HbA1c and WHR being confounders is strengthened by previous observations of the association of these factors with CRP (7,8,9) and also with diabetes risk (10,11,12,13,14). CRP originates in the liver and is increased in people with liver steatosis (15), suggesting a link between chronic inflammation and non-alcoholic fattyliver disease. It is possible that adiponectin may act as an intermediate between CRP and diabetes. Recent in vitro evidence suggests that CRP inhibits adiponectin gene expression in adipocytes (16), and this may lead to reduced insulin sensitivity and diabetes .Although the meta-analysis of 16 prospective studies showed an overall association between CRP levels and incident diabetes, these studies vary in certain characteristics. Visceral adipose tissue, compared with subcutaneous fat, is known to produce more pro-inflammatory cytokines (17) and is associated with CRP levels (18), suggesting that visceral adiposity could be an additional important confounding factor that was not considered in all studies.

Conclusion-

Our primary analysis of the case– control study suggests that there is association between CRP and risk of diabetes after taking into consideration a wide range of potentially confounding factors, including central adiposity, WHR, HbA1c. Our meta-analysis differs from a previous report in that we have converted effect estimates into a common measure and have focused on exploring sources of heterogeneity between studies. Our study also highlighted that the traditional approach of analysing the pattern of confounding in existing studies is a useful adjunct to alternative approaches for investigating causal inference through molecular epidemiological approaches.

Conflict of interest- none declared

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